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## **Evolocumab for Early Reduction of LDL-Cholesterol Levels in Patients with Acute Coronary Syndromes (EVOPACS)**

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**Short Title:** Evlocumab in patients with ACS

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**ABSTRACT**

**BACKGROUND** While guidelines recommend in-hospital initiation of high-intensity statin therapy in patients with acute coronary syndromes (ACS), low-density lipoprotein cholesterol (LDL-C) target levels are frequently not attained. Evolocumab, a rapidly acting, potent LDL-C-lowering drug, has not been studied in the acute phase of ACS.

**OBJECTIVES** To assess the feasibility, safety, and LDL-C lowering efficacy of evolocumab initiated during the in-hospital phase of ACS.

**METHODS** We conducted an investigator-initiated, randomized, double-blind, placebo-controlled trial involving 308 patients hospitalized for ACS with elevated LDL-C levels ( $\geq 1.8$  mmol/L on high-intensity statin for at least 4 weeks;  $\geq 2.3$  mmol/L on low- or moderate-intensity statin; or  $\geq 3.2$  mmol/L on no stable dose of statin). Patients were randomly assigned 1:1 to receive subcutaneous evolocumab 420mg or matching placebo, administered in-hospital and after 4 weeks, on top of atorvastatin 40mg. The primary endpoint was percentage change in calculated LDL-C from baseline to 8 weeks.

**RESULTS** Most patients (78.2%) had not been on previous statin treatment. Mean LDL-C levels decreased from 3.61 mmol/L to 0.79 mmol/L at week 8 in the evolocumab group, and from 3.42 mmol/L to 2.06 mmol/L in the placebo group; the difference in mean percentage change from baseline was -40.7% (95% CI: -45.2 to -36.2;  $p < 0.001$ ). LDL-C levels  $< 1.8$  mmol/L were achieved at week 8 by 95.7% of patients in the evolocumab group vs. 37.6% in the placebo group. Adverse events and centrally adjudicated cardiovascular events were similar in both groups.

**CONCLUSIONS** In this first randomized trial assessing a PCSK9 antibody in the very high-risk setting of ACS, evolocumab added to high-intensity statin therapy was well tolerated and resulted in substantial reduction in LDL-C levels, rendering  $> 95\%$  of patients within currently recommended target levels.

**CONDENSED ABSTRACT**

The EVOPACS randomized, placebo-controlled trial assessed the feasibility, safety, and LDL-C lowering efficacy of evolocumab on top of high-intensity statin in 308 patients hospitalized for ACS. The primary endpoint, percentage change in LDL-C from baseline to 8 weeks, was  $-77.1 \pm 15.8\%$  in the evolocumab group vs.  $-35.4 \pm 26.6\%$  in the placebo group ( $p < 0.001$ ). More patients achieved an LDL-C target  $< 1.8$  mmol/L at week 8 with evolocumab vs. placebo (95.7% vs. 37.6%). The treatment was well tolerated; adverse events as well as centrally adjudicated cardiovascular events were similar in both groups.

**Keywords:** Evolocumab; PCSK9 inhibitor; acute coronary syndrome; LDL-C

**Abbreviation list**

ACS = acute coronary syndrome

ASCVD = atherosclerotic cardiovascular disease

HDL = high density lipoprotein

hs-CRP = high-sensitivity C-reactive protein

LDL-C = low-density lipoprotein cholesterol

NSTE-ACS = Non-ST-elevation acute coronary syndrome

PCSK9 = proprotein convertase subtilisin/kexin type 9

STEMI = ST-elevation myocardial infarction

**Clinical trial Registration:** ClinicalTrials.gov Number: NCT03287609

## Introduction

Patients with acute coronary syndromes (ACS) are at increased risk of recurrent ischaemic events, particularly during the early period following the index event (1). Lowering low-density lipoprotein cholesterol (LDL-C) reduces cardiovascular morbidity and mortality in patients with atherosclerotic cardiovascular disease (ASCVD), with a magnitude of clinical benefit that is proportional to the reduction in LDL-C levels (2,3). In the context of ACS, early, in-hospital initiation of high-intensity statin treatment reduces the occurrence of early events and is recommended in current clinical practice guidelines (4,5). While additional favourable biologic effects of statins on inflammation, endothelial function and coagulation have been postulated to contribute to the early clinical benefit observed in the acute period after ACS (6), that benefit is believed to be mediated, at least in part, by the reduction of LDL-related risk. In view of the delayed onset of action of statins and the high risk of event recurrence during the first weeks after ACS, and because of the frequent failure of ACS patients to attain treatment targets with intensive statin therapy alone (7), rapid and more potent lowering of LDL-C to levels even below currently recommended targets might be of potential therapeutic benefit in this setting. Proprotein convertase subtilisin/kexin type 9 (PCSK9) antibodies have emerged as a new class of drugs that rapidly and effectively lower LDL-C levels. Evolocumab has been investigated in subjects without clinically evident ASCVD (8,9) or with stabilized ischaemic heart disease (10,11), and was shown to reduce major cardiovascular events in the context of secondary prevention (11). Notably, patients were included in the FOURIER trial from several months up to 11 years following a myocardial infarction (12). The feasibility, safety, and LDL-lowering efficacy of PCSK9 antibody treatment initiated in the very high-risk, acute (within days) phase of ACS are presently unknown.

Against this background, we conducted a randomized, placebo-controlled trial to assess evolocumab administered in-hospital on top of high-intensity statin therapy, compared with high-intensity statin therapy alone, in patients presenting with ACS.

## Methods

### *Study design and patients*

The study design has been previously described (13) and details are provided in the **Online Appendix**. Briefly, EVOPACS (NCT03287609) is an investigator-initiated, prospective, randomized, double-blind, placebo-controlled, parallel-group, phase III trial conducted at 7 Swiss sites. We included patients presenting with ACS whose LDL-C levels were either higher than guideline-recommended targets (4) despite prior high-intensity statin therapy, or were not projected to decrease below these targets under newly-initiated high-intensity statin therapy. The protocol was approved by the institutional ethics committees, and all study participants provided written informed consent.

Patients hospitalized for ACS [Non-ST-elevation ACS (NSTEMI) with symptom onset <72h or ST-elevation myocardial infarction (STEMI) with symptom onset <24h before screening] were potentially eligible. Inclusion and exclusion criteria are detailed in the **Online Appendix**. Screening was performed in stabilized patients upon hospital admission, and LDL-C was assessed locally at each site to determine eligibility. LDL-C levels at screening had to be  $\geq 1.8$  mmol/L (70 mg/dL) if patients were on stable (unchanged for  $\geq 4$  weeks before screening) treatment with high-intensity statin; or  $\geq 2.3$  mmol/L (90 mg/dL) in patients previously taking low- or moderate-intensity statin; or  $\geq 3.2$  mmol/L (125 mg/dL) in patients not on stable statin treatment. Allowed time intervals for study enrolment and study drug administration are summarized in **Online Figure 1**. Eligible patients were randomly assigned in a 1:1 ratio to

receive evolocumab 420 mg every 4 weeks or placebo.

#### *Procedures and study interventions*

The study drug was administered at baseline as early as possible (within  $\leq 24$  hours) following randomisation. Among patients who underwent clinically indicated coronary angiography (with or without revascularization), administration of the study drug before angiography was favoured whenever possible, but administration after coronary angiography was also allowed. Blood samples were obtained at baseline for assessment of fasting lipids. The second study drug administration was performed during a visit at 4 weeks, and the final clinical visit was scheduled at 8 weeks.

Patients in both groups were planned to receive atorvastatin 40mg/day throughout the study. For patients who had been on a more potent statin regimen (atorvastatin  $>40$ mg or rosuvastatin  $>20$ mg), the background therapy was atorvastatin 80mg/day. Measurement of lipid levels, adjustments to statin therapy, and addition of non-statin lipid-lowering therapies were discouraged throughout the study. Enrolled patients were treated for the ACS event in accordance with current guidelines, including medical treatment with or without coronary angiography and revascularization [percutaneous coronary intervention (PCI) or coronary artery bypass (CABG) surgery].

#### *Outcomes*

The primary endpoint was percentage change in calculated LDL-C from baseline to 8 weeks. Other efficacy lipid measurements included total cholesterol, non-high-density lipoprotein (HDL) cholesterol, triglycerides, HDL cholesterol, apolipoproteins B and A1, and lipoprotein(a). Fasting lipids at baseline, 4 weeks and 8 weeks were measured at a central core laboratory (Bern University Hospital, Bern, Switzerland). The LDL-C level was calculated with

the use of the Friedewald formula. Secondary endpoints were adverse events (AEs) and serious adverse events (SAEs) from baseline to 8 weeks. Cardiovascular events were adjudicated by an independent, blinded Clinical Events Committee (CEC) and included death, myocardial infarction, coronary revascularization, hospitalization for recurrent ACS, hospitalization for heart failure, and cerebrovascular events (stroke or transient ischaemic attack). Exploratory endpoints reported herein included change in inflammatory biomarkers [high-sensitivity C-reactive protein (hsCRP), interleukin (IL)-1 $\beta$ , IL-6] from baseline to 8 weeks.

### *Statistical analysis*

The study was designed as a superiority trial powered for the primary endpoint. Assuming an average LDL-C reduction of 30% in placebo (atorvastatin 40mg) arm and 44% in the active (evolocumab plus atorvastatin 40mg) arm, and adopting a common standard deviation of 36%, a total sample size of 280 patients would provide statistical power of 90% at 5% significance level. Anticipating a dropout rate of 10% at 8 weeks, enrolment of 308 patients was planned (154 per arm).

Comparisons of baseline characteristics were performed using t-tests, Fisher's exact tests, and chi-square tests. Efficacy and safety analyses were performed on the full analysis set, which included all randomized patients who received at least one dose of the study drug. Analysis of the primary endpoint was conducted with a linear mixed effects model adjusting for presence of stable statin treatment at baseline (within  $\geq 4$  weeks prior to screening) as a fixed effect, and study center as a random effect. Analysis was based on the intention-to-treat (ITT) principle. For safety outcomes, missing data were not imputed, and adverse events were summarized by treatment group using descriptive statistics with rate ratios from Mantel-Cox regression (first event of each type), or Poisson regression (number of events of each type),



with the time-at-risk equivalent to date of 8-week follow-up or death. Pre-specified subgroup analyses were performed in relation to pre-randomization statin treatment (yes/no), clinical presentation (STEMI vs. NSTEMI-ACS), age, gender, and baseline LDL-C  $\geq$  vs.  $<$  median. Tests are two-sided throughout and a p-value below 5% was considered as significant. Analyses were performed with Stata 15.1 (StataCorp LLC, TX77845, USA).

The study protocol was developed by the Steering Committee. The Clinical Trials Unit Bern, an academic research organization, monitored the progress of the trial, had full access to the complete database, and independently generated all analyses. The authors had full access to the data and vouch for the accuracy and completeness of the analyses as presented.

## Results

Out of 3,581 patients screened (**Online Table 1**), 308 patients were enrolled between January 23, 2018, and March 08, 2019 and randomly assigned to receive evolocumab (n=155) or placebo (n=153). The majority (62%) of enrolled patients were screened for study participation within  $<24$  hours of patient-reported symptom onset, and all within  $<72$  hours (**Online Figure 1**). Baseline patient characteristics were generally well balanced between groups (**Table 1**). Mean age was  $60.8 \pm 11.3$  years, 18.5% of patients were women, 14% had a history of previous myocardial infarction, and 2.6% had peripheral arterial disease. Most patients (78.2%) had not been on stable statin treatment in the previous 4 weeks (76.3% were on no statin at baseline; **Online Table 2**). Mean calculated LDL-C levels at baseline were  $3.51 \pm 0.97$  mmol/L. Treatment of the index ACS event included PCI (84.1%), medical therapy alone (8.8%), or CABG (7.1%).

One patient in the placebo group withdrew consent early and did not receive the study drug at baseline, leaving a full analysis set of 307 patients who received at least one dose of study drug. The final visit at 8 weeks occurred in 293 patients (95.1% of those randomised)

(**Figure 1** and **Online Table 3**). The proportion of patients receiving atorvastatin 40 or 80 mg was 94.8% at discharge, 95.5% at week 4, and 93.6% at week 8, without significant differences between groups (**Online Table 2** and **Online Figure 2**).

### *Efficacy*

Calculated LDL-C was available at baseline as well as at 8 weeks for assessment of the primary endpoint in 277 patients (90%) (**Figure 1**). Percentage change in calculated LDL-C from baseline to 8 weeks was  $-77.1 \pm 15.8\%$  in the evolocumab group (from a mean 3.61 mmol/L to 0.79 mmol/L) vs.  $-35.4 \pm 26.6\%$  in the placebo group (from a mean 3.42 mmol/L to 2.06 mmol/L), amounting to a last-squares mean difference of  $-40.7\%$  between groups (95% CI  $-45.2$  to  $-36.2$ ;  $p < 0.001$ ) (**Table 2** and **Online Figure 3**). Consistent changes were observed in a pre-specified analysis using multiple imputations for missing data (**Online Table 4**), as well as in an exploratory, previously published approach (11,14) using either calculated LDL-C, or directly measured LDL-C in cases of calculated LDL-C level  $< 40$  mg/dL or triglyceride level  $> 400$  mg/dL (available in 290 patients, 94.2% of all) (**Online Table 5**).

The reduction in LDL-C levels was evident at 4 weeks and maintained at 8 weeks (**Figure 2**). At 8 weeks, LDL-C was reduced to  $< 1.8$  mmol/L in 95.7% of patients in the evolocumab group as compared with 37.6% in the placebo group (**Central Illustration**). Subgroup analyses of the primary endpoint showed a greater percent reduction in calculated LDL-C with evolocumab vs. placebo among patients who had been on statin treatment (mean difference  $-55.8\%$ , 95% CI  $-70.1$  to  $-41.6$ ) compared with those not on statin treatment at baseline ( $-36.5\%$ , 95% CI  $-40.5$  to  $-32.5$ ;  $p$ -value for interaction  $< 0.001$ ), and consistently, a greater reduction in patients with LDL-C levels below median at baseline. LDL-C reductions were otherwise consistent in relation to type of ACS, gender, and age (**Online Figure 4**).

Evolocumab compared with placebo significantly reduced other atherogenic lipid particles, with reductions of 26.5% in total cholesterol, 34.2% in apolipoprotein B, 34.6% in non-HDL-C ( $p < 0.001$  for all comparisons), and 20% in triglycerides ( $p = 0.024$ ). Evolocumab raised HDL-C by 4.8% ( $p = 0.03$ ), without significant differences in changes in apolipoprotein A1 (**Table 2** and **Online Table 6**). We found a significantly greater absolute, but not relative reduction in lipoprotein(a) with evolocumab (**Online Table 6**).

### *Safety*

The percentage of patients who experienced adverse events, serious adverse events, and adverse events leading to study drug discontinuation were similar between groups (**Table 3**). Musculoskeletal pain was the most common reported adverse event, occurring in 9 patients (5.8%) in the evolocumab and 4 patients (2.6%) in the placebo group ( $p = 0.16$ ). Other common events were diarrhea (3.9% vs. 2.0%), local injection site reaction (3.2% vs. 2.0%), and nasopharyngitis (2.6% vs. 2.0%). ALT increase  $> 3 \times$  ULN was reported in 2 patients (1.3%) in each group. Serious adverse events occurred in 7.7% vs. 7.2% of patients in the evolocumab and placebo group, respectively, and adverse events that led to study drug discontinuation occurred in 1.3% vs. 2.0% of patients (**Online Tables 7 and 8**).

Two deaths were reported. A 75-year male patient presented with NSTEMI-ACS and was scheduled for CABG; the patient developed anterior STEMI on the day of scheduled surgery (study day 9), underwent emergent repeat coronary angiography (in cardiogenic shock) that showed acute occlusion of the proximal left anterior descending artery, and died during the intervention despite prolonged resuscitation. The second patient, a 76-year old male, presented with NSTEMI-ACS and underwent CABG combined with aortic valve replacement on study day 11. The patient developed a series of complications (intraoperative rupture of the aortic root and

right coronary ostium requiring composite graft implantation; two repeat surgical revisions for pericardial tamponade), developed progressive cardiogenic shock with multi-organ failure, and died 14 days after surgery (25 days after study enrolment). Both fatal events were in the evolocumab group, were judged to be unrelated to the study drug by the Data and Safety Monitoring Board, and adjudicated as cardiovascular death by the CEC (**Online Table 9**).

Adjudicated CV events did not differ significantly between groups. The majority of events included coronary revascularization procedures (72 patients), primarily planned staged procedures (32 patients in the evolocumab vs. 38 in the placebo group). Target-lesion revascularization was reported in one patient in the placebo group, and other, clinically indicated coronary revascularizations in two patients in the evolocumab group. Five patients (4 in the evolocumab group, including the two patients who died, and one in the placebo group) experienced recurrent MI (**Online Table 10**).

#### *Inflammatory biomarkers*

Mean levels of hsCRP decreased from baseline to 8 weeks from 6.6 mg/L to 2.5 mg/L, without significant differences between groups. Similarly, there was no difference in the change in IL-1 $\beta$  and IL-6 levels (**Table 4** and **Online Table 11**).

## **Discussion**

This study, the first reported trial of a PCSK9 inhibitor initiated in-hospital in patients presenting with ACS, showed that the addition of evolocumab 420mg once every 4 weeks to high-intensity statin, compared with high-intensity statin alone, resulted in substantially greater reduction in LDL-C levels after 8 weeks. Treatment with evolocumab lowered mean LDL-C levels from 3.61 mmol/L to 0.79 mmol/L as early as 4 weeks after the index event, and enabled >95% of patients to achieve guideline-recommended LDL-C targets. The treatment was well

tolerated during the short duration of the study, without significant imbalances in adverse events.

In patients presenting with ACS, the current paradigm for lipid management favours a stepwise approach consisting of early initiation of high-intensity statin, followed by subsequent addition of ezetimibe, and ultimately consideration of PCSK9 inhibitor treatment if LDL-C levels remain elevated (4,5). With this approach, ACS patients with markedly elevated LDL-C levels would be considered for PCSK9 inhibitor treatment only several months following their index event. However, it is during the early period after an ACS that the risk of recurrent ischaemic events is greatest (1). Early initiation of intensive statin therapy following an ACS has been shown to reduce the occurrence of early recurrent events – within 4 weeks in the PROVE IT trial (6) and within 16 weeks in the MIRACL trial (15). In view of the delayed onset of action of statins, and considering that ACS patients frequently present with markedly elevated LDL-C levels (16) and fail to achieve recommended treatment targets despite potent statin treatment, there is an unmet need for early, intensive reduction of atherogenic lipids in properly selected patients in this very high-risk clinical setting. The EVOPACS study tested a novel approach of very early, in-hospital initiation of evolocumab in patients who either had uncontrolled LDL-C levels despite pre-existing high-intensity statin treatment, or were not expected to reach the recommended treatment targets with such a treatment. The study met its primary endpoint and showed favourable safety and tolerability outcomes. Importantly, because the early clinical benefit of in-hospital initiation of statins in ACS patients is likely mediated by both lipid-lowering and other pleiotropic effects (6,15), the positive prognostic impact of statins in the acute post-ACS period cannot be directly extrapolated to PCSK9 antibodies. Therefore, whether early initiation of a PCSK9 inhibitor on top of a statin during the acute ACS phase might translate into an incremental clinical benefit remains to be determined in properly designed

studies.

The present results build upon previous studies that investigated PCSK9 monoclonal antibodies in individuals with hypercholesterolemia without known ASCVD (8), patients with statin intolerance (17) or familial hypercholesterolemia (9), and patients with stable manifestations of ASCVD (10,11). The FOURIER trial showed that evolocumab significantly reduced the risk of cardiovascular events in patients with ASCVD (11), with greater risk reduction observed in patients closer to their index MI; notably, the median interval between index MI and study enrolment ranged from 4 months up to 11 years in FOURIER (12). Along the same lines, the ODYSSEY OUTCOMES trial assessed the cardiovascular effects of alirocumab in patients at least 1 month (median 2.6 months) after an ACS (14).

The average 40.7% LDL-C reduction achieved with evolocumab vs. placebo in EVOPACS, as compared with approximately 60% in previous evolocumab trials (8-11,17), should be interpreted in light of essential differences regarding background statin treatment. Unlike previous studies, treatment with evolocumab could be initiated in EVOPACS in patients who were not taking statin at baseline. These patients amounted to 79% of all enrolled patients, and in fact reflect the majority of ACS patients in contemporary trials (18) and real-world clinical practice (16). This finding explains the considerably higher baseline LDL-C levels in EVOPACS compared with previous evolocumab studies, in which patients were already on optimized statin therapy at baseline. It also accounts for the 35.4% average reduction in LDL-C in the placebo group [as compared with practically no change in earlier investigations (11,14)], considering that the majority of placebo-treated patients had been statin-naïve and received high-dose atorvastatin during the study. Along these lines, the treatment effect of evolocumab on LDL-C was greater in the context of pre-existing statin therapy (i.e. a subgroup that resembles

patients in FOURIER and other evolocumab trials) compared with patients in whom evolocumab and statin were both initiated in the acute ACS setting (**Online Figure 4**). Focusing on the on-treatment LDL-C levels in the evolocumab plus atorvastatin group compared with the atorvastatin-only group (2.1 vs. 0.8 mmol/L), our findings are consistent with the LDL-C reduction seen in trials where evolocumab was added to stable lipid-lowering therapy (8-12, 17).

The incidence of adverse events was overall similar between groups during the short duration of the study. These results are consistent with safety and tolerability data from previous studies with evolocumab in more stable clinical settings. The rate of cardiovascular events was numerically higher in the evolocumab group but did not differ significantly between groups, and was comparable to contemporary ACS trials; these results need to be interpreted in view of the modest sample size as well as the inclusion of broadly representative ACS patients with frequent comorbidities. The majority of adjudicated events included staged coronary revascularization procedures, in line with current evidence supporting treatment of the culprit lesion during the index ACS event and intervention in other significant lesions within the subsequent days or weeks (19). It should be noted that the study was not powered for cardiovascular outcomes or serious adverse events, and the effect of evolocumab on such events in the early post-ACS period merits further investigation.

Previous studies showed no effect of PCSK9 antibodies on CRP levels (11). Because earlier statin trials found considerably larger reductions in CRP in the context of acute ACS (20) compared with more stable ASCVD manifestations or individuals in primary prevention (21), and in view of the pathobiological implication of the PCSK9 enzyme in vascular inflammation (22), we hypothesized that evolocumab might suppress inflammation in the ACS setting. Our exploratory analyses of inflammatory biomarkers did not confirm this hypothesis. In view of the

anti-inflammatory effects of statins as well as the association between greater reduction of CRP with statins and better clinical outcomes (20), the neutral effect of evolocumab on CRP levels found herein as well as in previous trials points to the potential added value of combining PCSK9 antibodies with statins as background therapy.

This study has several limitations. Although the week-8 clinical visit was performed in 95% of patients, amounting to half the attrition rate anticipated in our power analysis (10%), the primary endpoint could be analysed in 90% of patients. This was due to the fact that, unlike previous PCSK9 inhibitor studies that used calculated LDL-C as their primary endpoint (10), we had not pre-specified elevated triglyceride levels as an exclusion criterion, and the Friedewald equation could not be reliably applied in a number of patients at baseline and/or follow-up. However, an ancillary analysis that was available in 94.1% of all randomised patients, using directly measured LDL-C in cases of very high triglycerides or very low LDL-C, showed very consistent results. Although evolocumab reduces LDL-C levels rapidly (within days) (23), lipid levels were first measured 4 weeks after the first study drug administration; thus, we could not capture earlier effects of evolocumab in this study setting. Given the large number of endpoints measured, the potential of type I error cannot be definitively excluded. Finally, the study size was modest, and the study duration short; based on the present results, larger and longer-term studies should further investigate evolocumab in the acute ACS setting, also assessing potential effects on clinical outcomes.

## **Conclusions**

In patients presenting with ACS, evolocumab initiated in-hospital on top of high-intensity statin therapy was well tolerated and resulted in substantial reduction in LDL-C levels after 8 weeks. Treatment with evolocumab allowed rapid attainment of currently recommended target



levels by >95% of patients as compared with one third of placebo-treated patients.

## CLINICAL PERSPECTIVES

**Competency in medical knowledge:** In patients with ACS, early (in-hospital) initiation of evolocumab on top of high-intensity statin appears to be well tolerated and results in substantial reduction in LDL-C levels and rapid attainment of recommended LDL-C treatment targets.

**Translational outlook:** Further studies are needed to investigate whether very early LDL-C lowering treatment with PCSK9 antibodies added to statin therapy might translate to improved clinical outcomes following ACS.

## References

1. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;37:267-315.
2. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376:1670-81.
3. Koskinas KC, Siontis GCM, Piccolo R, et al. Effect of statins and nonstatin LDL-lowering medications on cardiovascular outcomes in secondary prevention: a meta-analysis of randomized trials. *Eur Heart J* 2018;39:1172-80.
4. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J* 2016;37:2999-3058.
5. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. *J Am Coll Cardiol* 2019;73:e285-e350.
6. Ray KK, Cannon CP, McCabe CH, et al. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes. Results from the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol* 2005;46:1405-10.
7. Reiner Ž, De Backer G, Fras Z, et al. Lipid lowering drug therapy in patients with coronary heart disease from 24 European countries. Findings from the EUROASPIRE IV survey. *Atherosclerosis* 2016;246:243-50.

8. Giugliano RP, Desai NR, Kohli P, et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, doseranging, phase 2 study. *Lancet* 2012;380:2007-17.
9. Raal FJ, Stein EA, Dufour R, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015;385:331-40.
10. Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;372:1500-9.
11. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376:1713-22.
12. Sabatine MS, De Ferrari GM, Giugliano RP, et al. Clinical Benefit of Evolocumab by Severity and Extent of Coronary Artery Disease. *Circulation* 2018;138:756-66.
13. Koskinas KC, Windecker S, Buhayer A, et al. Design of the randomized, placebo-controlled evolocumab for early reduction of LDL-cholesterol levels in patients with acute coronary syndromes (EVOPACS) trial. *Clin Cardiol* 2018;41:1513-20.
14. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med* 2018;379:2097-2107.
15. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes. *JAMA* 2001;285:1711-8.
16. Gencer B, Koskinas KC, Räber L, et al. Eligibility for PCSK9 Inhibitors According to American College of Cardiology (ACC) and European Society of Cardiology/European

Atherosclerosis Society (ESC/EAS) Guidelines After Acute Coronary Syndromes. *J Am Heart Assoc* 2017;6(11).

17. Stroes E, Colquhoun D, Sullivan D, et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. *J Am Coll Cardiol* 2014;63:2541-8.

18. Berwanger O, Santucci EV, de Barros E, et al. Effect of Loading Dose of Atorvastatin Prior to Planned Percutaneous Coronary Intervention on Major Adverse Cardiovascular Events in Acute Coronary Syndrome: The SECURE-PCI Randomized Clinical Trial. *JAMA* 2018;319:1331-40.

19. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019;40:87-165.

20. Ridker PM, Cannon CP, Morrow D, et al. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med* 2005;352:20-8.

21. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195-207.

22. Ferri N, Tibolla G, Pirillo A, et al. Proprotein convertase subtilisin kexin type 9 (PCSK9) secreted by cultured smooth muscle cells reduces macrophages LDLR levels. *Atherosclerosis* 2012;220:381-6.

23. Dias CS, Shaywitz AJ, Wasserman SM, et al. Effects of AMG 145 on low-density lipoprotein cholesterol levels: results from 2 randomized, double-blind, placebo-controlled, ascending-dose phase 1 studies in healthy volunteers and hypercholesterolemic subjects on statins. *J Am Coll Cardiol*. 2012;60:1888-98.

## Figure Legends

**Central Illustration. Attainment of the LDL-C Treatment Target <1.8 mmol/L at 8 Weeks in ACS Patients Receiving Evolocumab or Placebo on Top of High-Intensity Statin.** Patients presenting with ACS and elevated LDL-C levels received either guideline-recommended high-intensity statin plus placebo sc, or high-intensity statin plus evolocumab sc. At 8 weeks, more than 95% of evolocumab-treated patients had an LDL-C level <1.8 mmol/l as compared with one third of placebo-treated patients. The impact of early (in-hospital) initiation of PCSK9 antibody treatment added to statin on cardiovascular outcomes requires further investigation.

Abbreviations: ACS = acute coronary syndrome; LDL-C = low-density lipoprotein cholesterol.

**Figure 1: Study Flowchart.** Reasons for exclusion of patients are detailed in **Online Table 1**.

AE = adverse event; LDL-C = low-density lipoprotein cholesterol.

**Figure 2: Changes in LDL-Cholesterol Levels over Time.** (A) Shown are mean values in the two study groups; error bars indicate 95% confidence intervals. Below the graph, the absolute and percentage reductions in calculated LDL-cholesterol level in the evolocumab group are compared with those in the placebo group, presented as least-squares means. (B) Mean percentage changes in calculated LDL-cholesterol ( $\pm$  standard deviations) from baseline to 4 weeks and 8 weeks in the two study groups.

**Table 1 Baseline Characteristics**

	<b>Evolocumab (n=155)</b>	<b>Placebo (n=153)</b>
Age (years)	60.5±12.0	61.0±10.7
Male gender, n (%)	128 (83)	123 (80)
Body mass index (kg/m <sup>2</sup> )	26.9±4.0	27.8±3.9
Diabetes mellitus, n (%)	23 (15)	24 (16)
Insulin-treated	1 (1)	6 (4)
Arterial hypertension, n (%)	79 (51)	85 (56)
Active smoking, n (%)	64 (41)	46 (30)
Previous myocardial infarction, n (%)	24 (15)	19 (12)
Previous PCI, n (%)	25 (16)	23 (15)
Previous CABG, n (%)	5 (3)	4 (3)
Peripheral arterial disease, n (%)	4 (3)	4 (3)
History of stroke, n (%)	2 (1)	0 (0)
History of TIA, n (%)	5 (3)	0 (0)
History of malignancy, n (%)	13 (8)	10 (7)
Statin treatment*, n (%)		
No statin	124 (80)	117 (76)
Low- or moderate-intensity statin	13 (8)	22 (14)
High-intensity statin <sup>†</sup>	18 (12)	14 (9)
Ezetimibe treatment, n (%)	6 (4)	9 (6)
Time of symptom onset <24h, n (%)	100 (65)	90 (59)
Index ACS event, n (%)		
NSTEMI-ACS	88 (57)	107 (70)
STEMI	67 (43)	46 (30)

ACS = acute coronary syndrome; CABG = coronary artery bypass graft surgery; NSTEMI-ACS = non-ST-elevation acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction; TIA = transient ischaemic stroke.

\* Stable (unchanged) in the past ≥4 weeks prior to study enrolment.

<sup>†</sup> Atorvastatin ≥40mg, rosuvastatin ≥20mg, or simvastatin 80mg.

**Table 2 Efficacy Outcomes**

	<b>Evolocumab</b>	<b>Placebo</b>	<b>Mean difference (95% CI)*</b>	<b>p value</b>
<b>Calculated LDL-C</b>				
Baseline (mmol/L)	3.61±1.00 [146]	3.42±0.94 [148]	0.14 (-0.05 to 0.32)	
Week 8 (mmol/L)	0.79±0.46 [141]	2.06±0.63 [149]	-1.27 (-1.40 to -1.14)	<0.001
Absolute change from baseline (mmol/L)	-2.83±1.02 [132]	-1.35±1.04 [145]	-1.43 (-1.63 to -1.22)	<0.001
% Change from baseline (primary endpoint)	-77.1%±15.8% [132]	-35.4%±26.6% [145]	-40.7% (-45.2% to -36.2%)	<0.001
Calculated LDL-C <1.8 mmol/L at week 8, %	95.7% [141]	37.6% [149]	57.8% (66.2% to 49.4%)	<0.001
<b>Other lipids, % change from baseline to week 8</b>				
Cholesterol	-51.8%±14.6% [140]	-24.4%±19.3% [150]	-26.5% (-29.9% to -23.1%)	<0.001
Apolipoprotein B	-63.6%±14.9% [137]	-28.8%±23.4% [149]	-34.2% (-38.2% to -30.2%)	<0.001
Non-HDL-C	-67.3%±15.4% [140]	-31.7%±23.7% [150]	-34.6% (-38.5% to -30.6%)	<0.001
Triglycerides	-16.4%±40.4% [140]	4.5%±98.4% [150]	-20.0% (-37.4% to -2.6%)	0.024
HDL-C	9.5%±17.9% [140]	4.9%±19.7% [150]	4.8% (0.5 to 9.1%)	0.03
Apolipoprotein A1	5.6%±15.5% [137]	3.5%±14.7% [148]	2.2% (-1.2% to 5.7%)	0.21
Lipoprotein(a)	0.5%±67.6% [139]	10.4%±49.5% [150]	-10.4% (-38.3% to 17.6%)	0.47

Data expressed as means or least-squares means ± standard deviations, or n (%). P-value of the randomized arm, using mixed models correcting for a random effect of study site and a fixed effect of stable statin treatment before randomization.

\*Evolocumab minus placebo.



**Table 3 Adverse Events**

	<b>Evolocumab (n=155)</b>	<b>Placebo (n=152)*</b>	<b>p value</b>
Any adverse event	78 (50.3)	77 (50.7)	0.72
Serious adverse event	12 (7.7)	11 (7.2)	0.84
Adverse event resulting in study drug discontinuation	2 (1.3)	3 (2.0)	0.65
Events of special interest			
ALT increase >3xULN	2 (1.3)	2 (1.3)	0.97
Symptomatic overdose	0 (0.0)	0 (0.0)	
General allergic reaction	1 (0.6)	0 (0.0)	1.00
Local injection site reaction	5 (3.2)	3 (2.0)	0.48
Pregnancy	0 (0.0)	0 (0.0)	
Neurocognitive event	1 (0.6)	0 (0.0)	1.00
Musculoskeletal pain	9 (5.8)	4 (2.6)	0.16
Nasopharyngitis	4 (2.6)	3 (2.0)	0.71
Diarrhoea	6 (3.9)	3 (2.0)	0.30
Other	63 (40.6)	64 (42.1)	0.91
Positively adjudicated events			
All-cause death	2 (1.3)	0 (0.0)	0.50
Cardiovascular death	2 (1.3)	0 (0.0)	0.50
Myocardial infarction	4 (2.6) <sup>†</sup>	1 (0.7)	0.17
Coronary revascularization	33 (21.3)	39 (25.7)	0.39
Target-lesion revascularization	0 (0.0)	1 (0.7)	0.50
Planned staged procedure	32 (20.6)	38 (25.0)	0.39
Other revascularization	2 (1.3)	0 (0.0)	0.50
Cerebrovascular event (stroke / TIA)	1 (0.6)	0 (0.0)	1.00
Hospitalization for recurrent ACS	0 (0.0)	1 (0.7)	0.50
Hospitalization for heart failure	0 (0.0)	0 (0.0)	

Number (proportion) of patients with each event type are reported, not counting multiple events of the same type. Fisher's exact tests in case of zero events in one group.

ACS = acute coronary syndrome; ALT = alanine aminotransferase; TIA = transient ischaemic attack; ULN = upper limit of normal.

\*Excluded is one patient randomly allocated to placebo who withdrew consent early and refused study drug injection and any study intervention.

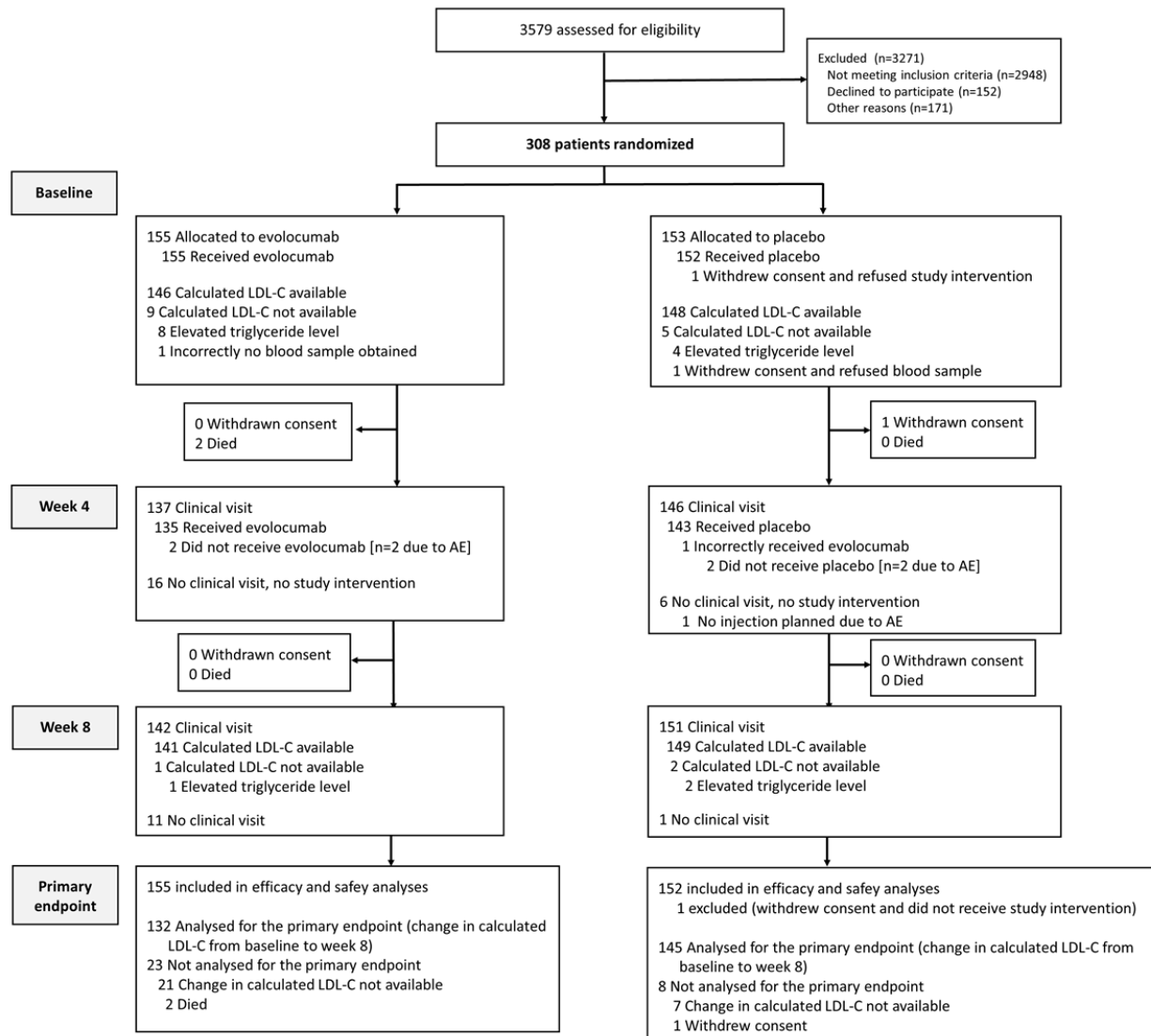
<sup>†</sup>Including two patients who died.

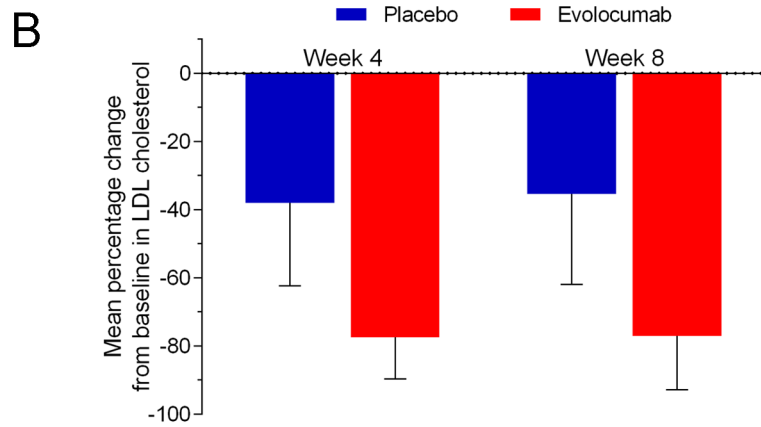
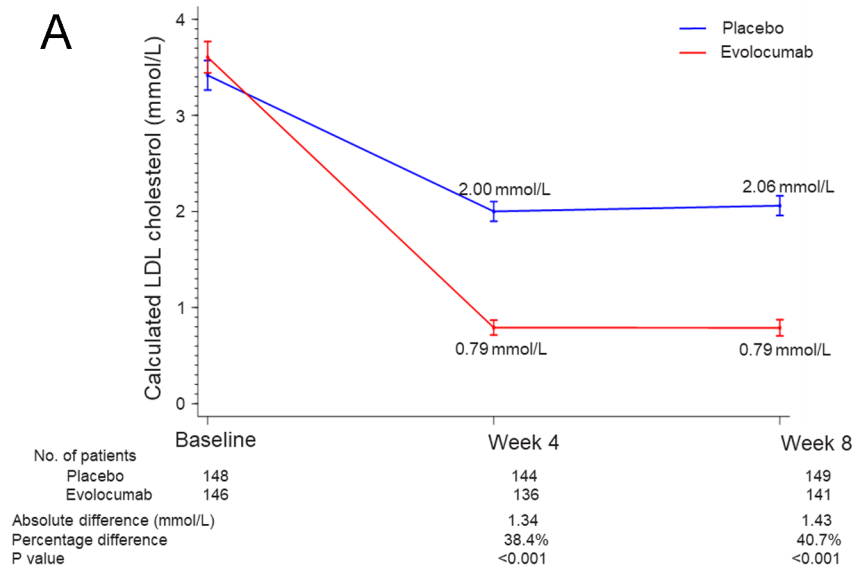
**TABLE 4 Inflammatory Biomarkers**

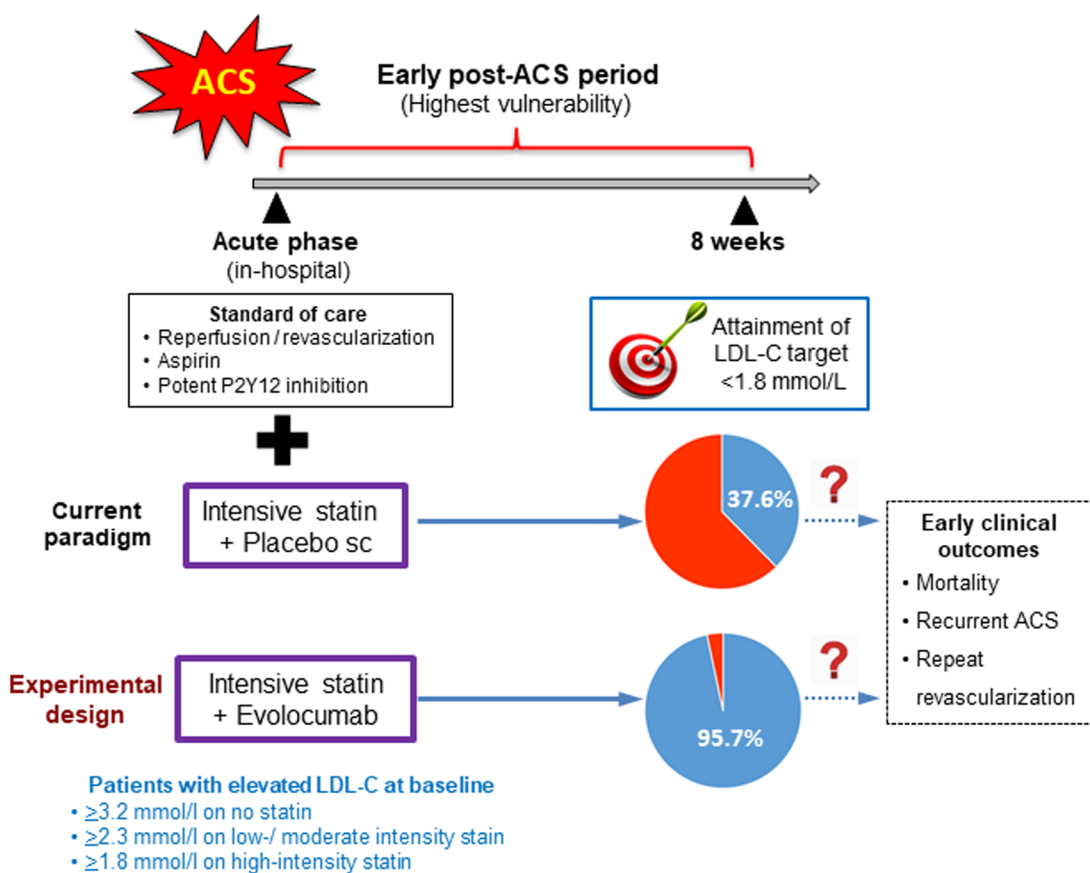
	<b>Evolocumab (155)</b>	<b>Placebo (152)</b>	<b>Mean difference<sup>*</sup> (95% CI)</b>	<b>p value</b>
Inflammatory biomarkers (change from baseline to week 8)				
% Change hsCRP	-14.9±255.7	-35.1±111.7	19.6 (-25.2 to 64.5)	0.39
hs-CRP level <2 mg/L at week 8 (%)	68.8%	69.3%	-0.7 (-11.4 to 9.9)	0.89
Change in interleukin-1 $\beta$ (pg/ml)	0.05±0.90	-0.01±0.89	0.06 (-0.14 to 0.27)	0.53
Change in interleukin 6 (pg/ml)	9.95±14.62	9.34±15.23	0.59 (-2.87 to 4.05)	0.74

hsCRP = high-sensitivity C-reacting protein.

<sup>\*</sup>Evolocumab minus placebo







**Evolocumab for early reduction of LDL-cholesterol levels in patients with acute coronary syndromes (EVOPACS): a randomised, double-blind, placebo-controlled trial**

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**Online Appendix**

## Supplemental Methods

### 1. Patient eligibility

#### Inclusion Criteria

- Male or female  $\geq 18$  years of age
- Hospitalized for a recent ACS (unstable angina or NSTEMI within  $< 72$  hours, STEMI within  $< 24$  hours prior to screening)
- LDL-C levels defined as follows:
  - LDL-C  $\geq 70$  mg/dL ( $\geq 1.8$  mmol/L) or non-HDL-C  $\geq 100$  mg/dL ( $\geq 2.6$  mmol/L) in patients who have been receiving stable treatment with high-intensity statin within  $\geq 4$  weeks prior to enrollment (i.e. continuous treatment that has not changed with regard to statin intensity over the past 4 weeks)
  - LDL-C  $\geq 90$  mg/dL ( $\geq 2.3$  mmol/L) or non-HDL-C  $\geq 120$  mg/dL ( $\geq 3.1$  mmol/L) in patients who have been receiving stable treatment with low- or moderate-intensity statin within  $\geq 4$  weeks prior to enrollment (i.e. continuous treatment that has not changed with regard to statin intensity over the past 4 weeks)
  - LDL-C  $\geq 125$  mg/dL ( $\geq 3.2$  mmol/L) or non-HDL-C  $\geq 155$  mg/dL ( $\geq 4.0$  mmol/L) in patients who are statin-naïve or have not been on a stable (unchanged) statin regimen for at least 4 weeks prior to enrollment.
- Ability to understand the requirements of the study and to provide informed consent

#### Exclusion criteria

- Unstable clinical status (hemodynamic or electrical instability)
- Uncontrolled cardiac arrhythmia, defined as recurrent and symptomatic ventricular tachycardia or atrial fibrillation or flutter with rapid ventricular response not controlled by medications in the past 3 months prior to screening
- Severe renal dysfunction, defined by estimated glomerular filtration rate  $< 30$  ml/min/1.73m<sup>2</sup>
- Active liver disease or hepatic dysfunction, either reported in patient medical record or defined by aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels  $> 3$ x the upper limit of normal.
- Reported intolerance to atorvastatin (any dose) OR statin intolerance defined by the following criteria: inability to tolerate at least 2 different statins (one statin at the lowest starting average daily dose and the other statin at any dose); intolerance associated with confirmed, intolerable statin-related adverse effect(s) or significant biomarker abnormalities; symptom or biomarker changes resolution or significant improvement upon dose decrease or discontinuation; and symptoms or biomarker changes not attributable to established predispositions such as drug-drug interactions and recognized conditions increasing the risk of statin intolerance
- Known allergy to contrast medium, heparin, aspirin, ticagrelor or prasugrel
- Known sensitivity to any substances to be administered
- Patients who previously received evolocumab or other PCSK9 inhibitor
- Patient who received cholesterol ester transfer protein inhibitors in the past 12 months prior to screening

- Treatment with systemic steroids or systemic cyclosporine in the past 3 months (e.g. intravenous, intramuscular or per os)
- Known active infection or major hematologic, metabolic, or endocrine dysfunction in the judgment of the Investigator
- Patients who will not be available for study-required procedures in the judgment of the Investigator
- Current enrollment in another investigational device or drug study
- Active malignancy requiring treatment
- Pregnant women. For female of childbearing potential (age <50 years and last menstruation within the last 12 months), who did not undergo tubal ligation, ovariectomy or hysterectomy, pregnancy is excluded by a pregnancy test prior to inclusion in the study.

The rationale for the LDL-C eligibility thresholds in conjunction with pre-enrollment statin treatment status relates to the inclusion of patients who had not reached the guideline-recommended LDL-C target of 70 mg/dL (1.8 mmol/L)<sup>1</sup> prior to screening while on previous statin treatment, or were not expected to reach the target with the effect of atorvastatin 40mg QD (background statin therapy for all patients during the study period). Thereby, additional lipid-lowering (evolocumab in the active treatment group) would be justified in these patients. The threshold of LDL-C levels 90mg/dL (2.3 mmol/L) in patients who had been on low- or moderate intensity statin reflects the anticipated incremental LDL-C reduction when switching from low- or moderate statin (prior to enrollment) to atorvastatin 40mg QD during the study (estimated, on average, 22% incremental LDL-C reduction).<sup>2</sup> Similarly, the LDL-C threshold of 125 mg/dL (3.2 mmol/L) accounts for the LDL-C lowering effect of atorvastatin 40mg QD by 43%<sup>2</sup>; hence, in patients with LDL-C levels  $\geq 125$  mg/dl (3.2 mmol) without pre-enrollment stable statin treatment, LDL-C levels would still remain above target despite the expected effect of atorvastatin 40mg, and additional LDL-C-lowering by means of evolocumab would be justified.

## 2. Randomisation and masking

Eligible patients were randomly assigned in a 1:1 ratio to receive subcutaneous evolocumab 420 mg every 4 weeks or placebo. Allocation sequences were based on computer-generated random numbers. Sequences were generated by an independent statistician and concealed using a central randomization system. To ensure a balanced allocation of treatment and control over time, randomization lists were generated in blocks of 2, 4, or 6 patients and to enforce concealment, block size was generated at random. Randomization was stratified according to study center, and presence of stable statin treatment within  $\geq 4$  weeks prior to enrollment (yes/no). Patients, investigators, study personnel, and adjudicators were masked to treatment assignment. The members of the Data and Safety Monitoring Board (DSMB) had access to unmasked data. Masking of the study drug was accomplished by use of identical pens with solutions for injection that were indistinguishable in appearance.

## References

1. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J 2016;37(39):2999-3058.

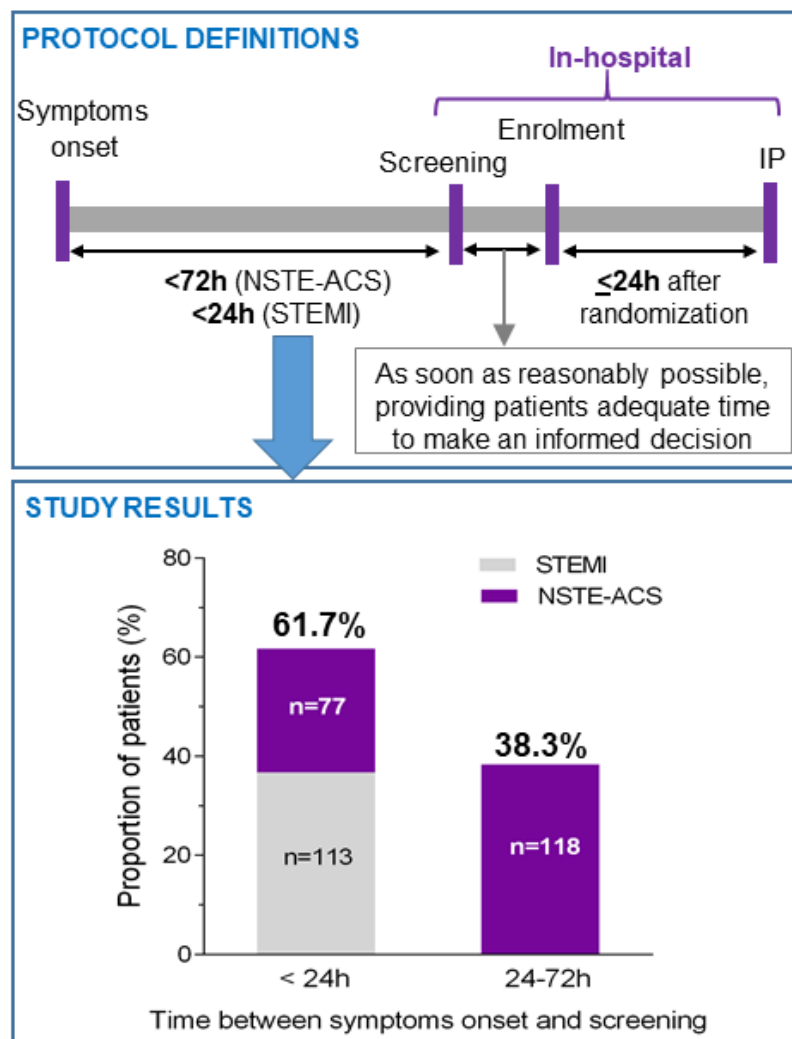


2. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2016;68:92-125.

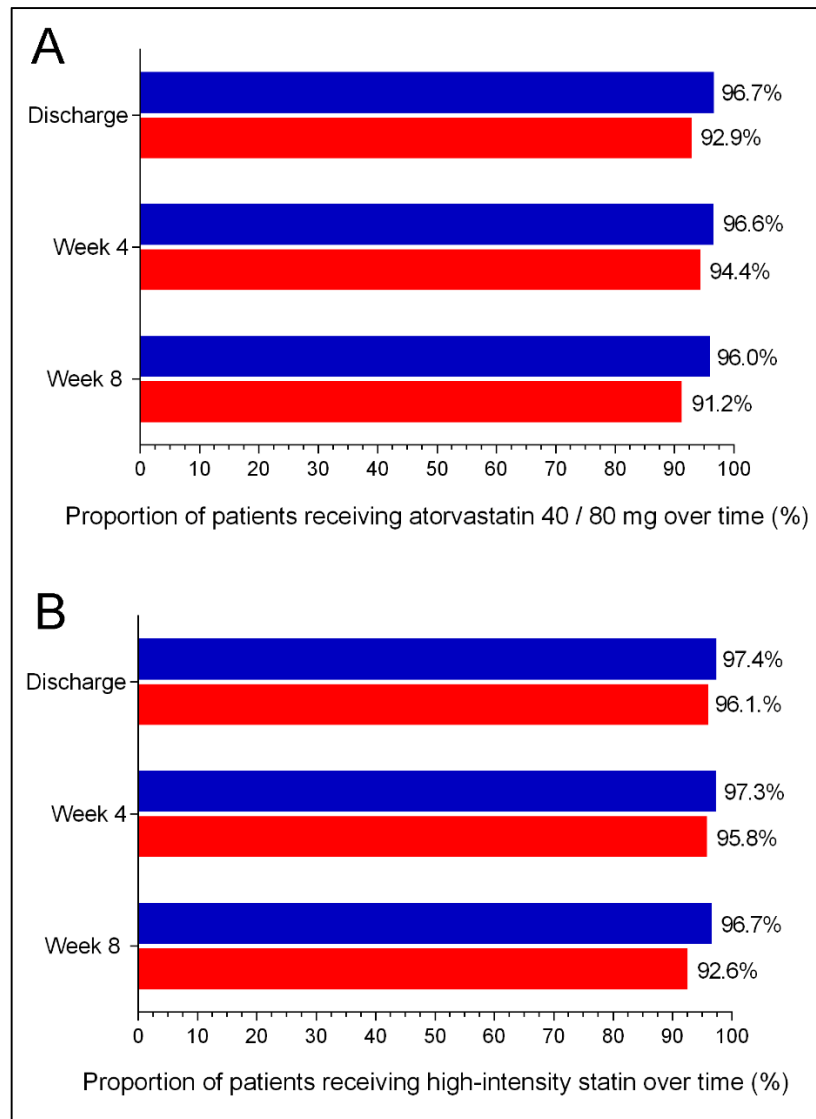
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## Appendix Figures

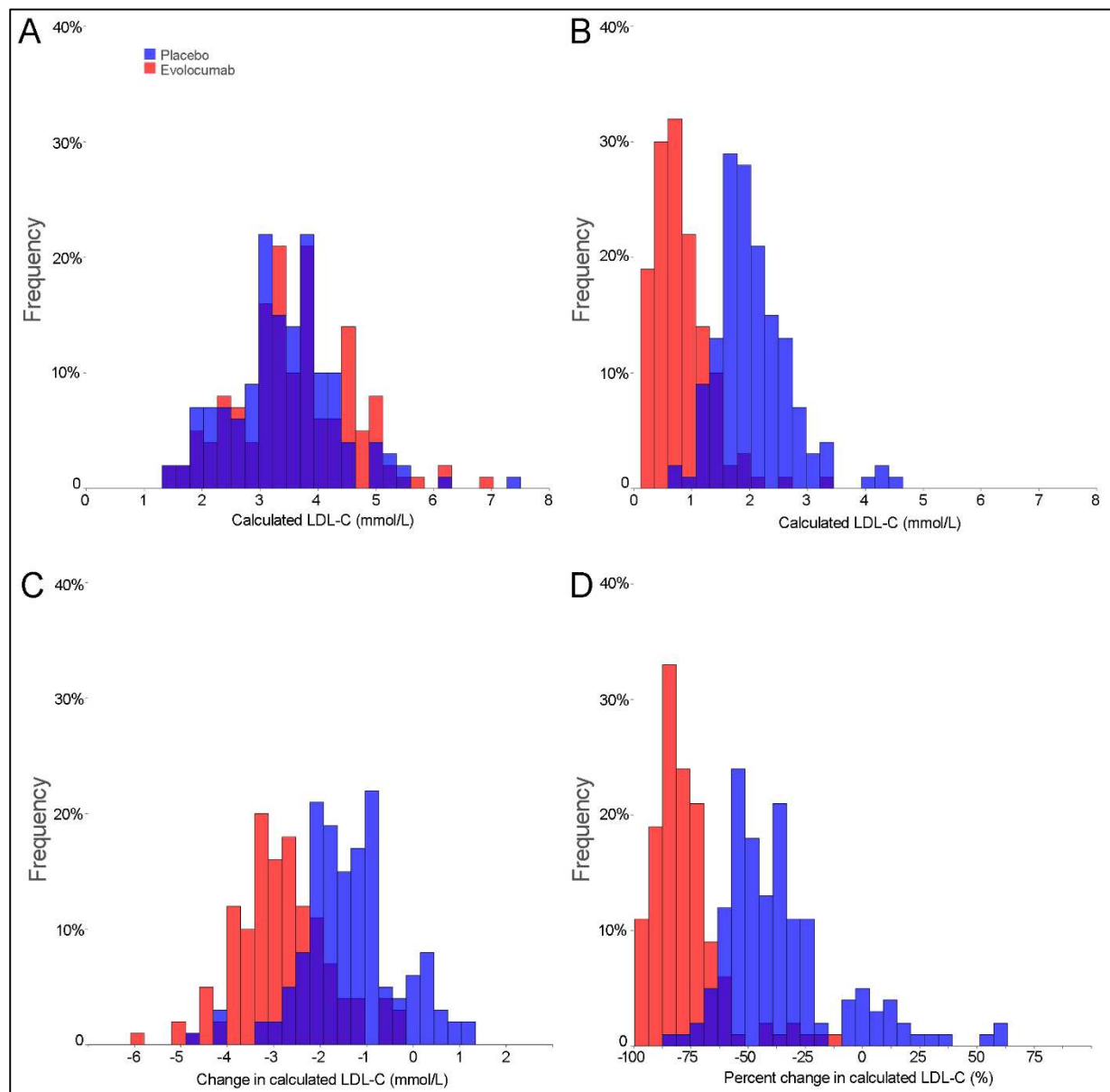
**Appendix Figure 1.** Upper panel: Protocol-defined time windows for enrolment and administration of the investigational product (IP) at baseline in relation to the time of onset of symptoms in patients presenting with acute coronary syndromes (ACS). Lower panel: shown are the proportions of patients who were screened for study enrolment within <24 hours or between 24 and 72 hours of symptoms onset, stratified by type of ASC (STEMI vs. NSTEMI-ACS).



**Appendix Figure 2.** Proportion of patients receiving the protocol-defined statin regimen, atorvastatin 40 or 80 mg (**A**); or high-intensity statin (**B**) over time. Blue color indicates the placebo group, and red color the evolocumab group. There were no significant differences between the two treatment groups at any time point (see **Appendix Table 2**).



**Appendix Figure 3.** Frequency distribution of calculated LDL-C levels at baseline (A) and 8 weeks (B), absolute change (C), and percentage change (D) in calculated LDL-C between baseline and 8 weeks in the placebo and evolocumab groups.



**Appendix Figure 4.** Subgroup analyses for the primary endpoint, percentage change in calculated LDL-C from baseline to 8 weeks, in relation to statin treatment at baseline; study center; type of ACS (STEMI vs. NSTEMI-ACS); age; gender; and calculated LDL-C at baseline  $\geq$  vs.  $<$  the median. Stratification for baseline statin treatment was done according to presence or absence of stable (unchanged) statin treatment in the preceding 4 weeks prior to enrolment. Shown are means  $\pm$  standard deviations (p-value from mixed models), interaction p-value testing for the interaction effect subgroup x randomised arm from full-factorial mixed model.

	Evolocumab		Placebo		Calculated LDL-C Mean difference (95% CI)	Mean difference (95% CI)	p-value	interaction p-value
	n=155	mean $\pm$ sd	n=152	mean $\pm$ sd				
<b>Overall</b>	n=132	-77.07 $\pm$ 15.78 [132]	n=145	-35.38 $\pm$ 26.61 [145]		-40.7 (-45.2 to -36.2)	<0.001	
<b>Statin at baseline</b>								<0.001
yes	n=26	-63.89 $\pm$ 24.83 [26]	n=34	-8.05 $\pm$ 30.81 [34]		-55.8 (-70.1 to -41.6)	<0.001	
no	n=106	-80.30 $\pm$ 10.50 [106]	n=111	-43.75 $\pm$ 18.46 [111]		-36.5 (-40.5 to -32.5)	<0.001	
<b>Study center</b>								0.50
#1	n=45	-75.05 $\pm$ 17.88 [45]	n=48	-38.94 $\pm$ 23.84 [48]		-35.0 (-42.2 to -27.9)	<0.001	
#2	n=6	-73.04 $\pm$ 16.97 [6]	n=8	-44.08 $\pm$ 9.47 [8]		-33.4 (-42.9 to -24.0)	<0.001	
#3	n=5	-79.15 $\pm$ 3.86 [5]	n=7	-26.23 $\pm$ 44.27 [7]		-42.9 (-71.4 to -14.4)	0.003	
#4	n=41	-79.22 $\pm$ 12.27 [41]	n=46	-35.93 $\pm$ 26.52 [46]		-42.8 (-50.7 to -35.0)	<0.001	
#5	n=4	-66.25 $\pm$ 31.79 [4]	n=2	-3.27 $\pm$ 36.05 [2]		-59.2 (-104.8 to -13.7)	0.011	
#6	n=24	-78.96 $\pm$ 16.09 [24]	n=25	-29.02 $\pm$ 27.52 [25]		-47.6 (-59.0 to -36.2)	<0.001	
#7	n=7	-79.08 $\pm$ 12.67 [7]	n=9	-37.76 $\pm$ 29.20 [9]		-43.7 (-58.6 to -28.8)	<0.001	
<b>Clinical presentation</b>								0.42
STEMI	n=58	-80.52 $\pm$ 12.83 [58]	n=45	-42.68 $\pm$ 21.15 [45]		-37.8 (-44.4 to -31.3)	<0.001	
NSTEMI-ACS	n=74	-74.36 $\pm$ 17.36 [74]	n=100	-32.09 $\pm$ 28.21 [100]		-42.3 (-49.5 to -35.0)	<0.001	
<b>Age</b>								0.90
<65years	n=89	-78.88 $\pm$ 13.90 [89]	n=95	-37.05 $\pm$ 26.83 [95]		-41.8 (-48.0 to -35.6)	<0.001	
$\geq$ 65years	n=43	-73.31 $\pm$ 18.72 [43]	n=50	-32.21 $\pm$ 26.17 [50]		-41.1 (-50.4 to -31.8)	<0.001	
<b>Gender</b>								0.69
male	n=109	-78.08 $\pm$ 15.80 [109]	n=116	-35.99 $\pm$ 26.41 [116]		-42.1 (-47.8 to -36.4)	<0.001	
female	n=23	-72.26 $\pm$ 15.11 [23]	n=29	-32.93 $\pm$ 27.72 [29]		-39.3 (-51.7 to -27.0)	<0.001	
<b>LDL-C at baseline</b>								0.01
$\geq$ median	n=70	-80.86 $\pm$ 10.64 [70]	n=69	-46.26 $\pm$ 16.21 [69]		-34.6 (-39.1 to -30.1)	<0.001	
< median	n=62	-72.78 $\pm$ 19.28 [62]	n=76	-25.50 $\pm$ 30.22 [76]		-47.3 (-55.9 to -38.7)	<0.001	

### Appendix Tables

**Appendix Table 1.** Reasons for not enrolling screened patients

<b>Reason</b>	<b>Number</b>
Screening LDL-C levels not meeting the protocol-defined criteria	1,010
Index ACS event not meeting the protocol definition (NSTEMI-ACS with symptoms onset within $\leq 72$ hours, STEMI with symptoms onset within $\leq 24$ hours prior to screening)	723
Unstable clinical status (hemodynamic or electrical instability)	250
Patients would not be available for study-required procedures in the judgment of the investigator	243
Current enrollment in another investigational device or drug study	151
Active liver disease or hepatic dysfunction according to protocol criteria	118
Severe renal dysfunction	93
Treatment with systemic steroids or systemic cyclosporine in the past 3 months	83
Active malignancy requiring treatment	77
Known active infection or major hematologic, metabolic, or endocrine dysfunction in the judgment of the investigator	71
Intolerance to atorvastatin or statin intolerance according to protocol criteria	43
No ability to understand the requirements of the study and provide informed consent in the judgment of the investigator	27
Known sensitivity to any substances to be administered during the study	25
Known allergy to contrast medium, heparin, aspirin, ticagrelor or prasugrel	13
Uncontrolled cardiac arrhythmia	12
Patients who previously received evolocumab or other PCSK9 inhibitor	9
Patient refusal	152
Other reasons	171
<b>Total</b>	<b>3,271</b>

**Appendix Table 2.** Lipid-lowering and antithrombotic medications at baseline and throughout the study

	All patients	Evolocumab	Placebo	<i>P</i> -value
Baseline, n (%)	n=308	n=155	n=153	
Statin treatment				0.03
No statin	235 (76)	121 (78)	114 (75)	0.50
Low-intensity statin	5 (2)	4 (3)	1 (1)	0.37
Moderate-intensity statin	32 (10)	9 (6)	23 (15)	0.009
High-intensity statin	36 (12)	21 (14)	15 (10)	0.38
Other lipid-lowering drugs				
Ezetimibe	15 (5)	6 (4)	9 (6)	0.44
Fibrates	0 (0)	0 (0)	0 (0)	
Niacin	0 (0)	0 (0)	0 (0)	
Resins	1 (0)	1 (1)	0 (0)	1.00
Aspirin	74 (24)	38 (25)	36 (24)	0.89
Clopidogrel	9 (3)	4 (3)	5 (3)	0.75
Ticagrelor	4 (1)	2 (1)	2 (1)	1.00
Prasugrel	2 (1)	0 (0)	2 (1)	0.25
Dipyridamole	0 (0)	0 (0)	0 (0)	
NOAC	6 (2)	5 (3)	1 (1)	0.21
Vitamin K antagonists	4 (1)	2 (1)	2 (1)	1.00
Discharge, n (%)	n=306	n=154	n=152	
Statin treatment				0.53
No statin	5 (2)	2 (1)	3 (2)	0.68
Low-intensity statin	1 (0)	1 (1)	0 (0)	1.00
Moderate-intensity statin	4 (1)	3 (2)	1 (1)	0.62
High-intensity statin	296 (97)	148 (96)	148 (97)	0.75
Atorvastatin 40mg	283 (92)	139 (90)	144 (95)	0.19
Atorvastatin 40 or 80mg	290 (95)	143 (93)	147 (97)	0.20
Other lipid-lowering drugs				
Ezetimibe	7 (2)	5 (3)	2 (1)	0.45
Fibrates	0 (0)	0 (0)	0 (0)	
Niacin	0 (0)	0 (0)	0 (0)	
Resins	1 (0)	1 (1)	0 (0)	1.00
Aspirin	293 (96)	146 (95)	147 (97)	0.57
Clopidogrel	30 (10)	18 (12)	12 (8)	0.34
Ticagrelor	214 (70)	104 (68)	110 (72)	0.38
Prasugrel	35 (11)	16 (10)	19 (13)	0.59
NOAC	13 (4)	9 (6)	4 (3)	0.26
Vitamin K antagonists	8 (3)	4 (3)	4 (3)	1.00

<b>Week 4, n (%)</b>	<b>n=291</b>	<b>n=144</b>	<b>n=147</b>	
Statin treatment				0.56
No statin	6 (2)	4 (3)	2 (1)	0.44
Low-intensity statin	1 (0)	1 (1)	0 (0)	0.49
Moderate-intensity statin	3 (1)	1 (1)	2 (1)	1.00
High-intensity statin	281 (97)	138 (96)	143 (97)	0.54
Atorvastatin 40mg	273 (94)	135 (94)	138 (94)	1.00
Atorvastatin 40 or 80 mg	278 (96)	136 (94)	142 (97)	0.41
Other lipid-lowering drugs				
Ezetimibe	8 (3)	4 (3)	4 (3)	1.00
Fibrates	0 (0)	0 (0)	0 (0)	
Niacin	0 (0)	0 (0)	0 (0)	
Resins	0 (0)	0 (0)	0 (0)	
Aspirin	278 (96)	136 (94)	142 (97)	0.41
Clopidogrel	33 (11)	18 (13)	15 (10)	0.58
Ticagrelor	198 (68)	93 (65)	105 (71)	0.26
Prasugrel	36 (12)	18 (13)	18 (12)	1.00
NOAC	18 (6)	13 (9)	5 (3)	0.054
Vitamin K antagonists	7 (2)	3 (2)	4 (3)	1.00
<b>Week 8, n (%)</b>	<b>n=299</b>	<b>n=148</b>	<b>n=151</b>	
Statin treatment				0.26
No statin	9 (3)	7 (5)	2 (1)	0.10
Low-intensity statin	1 (0)	1 (1)	0 (0)	0.49
Moderate-intensity statin	6 (2)	3 (2)	3 (2)	1.00
High-intensity statin	283 (95)	137 (93)	146 (97)	0.13
Atorvastatin 40mg	273 (91)	133 (90)	140 (93)	0.42
Atorvastatin 40 or 80 mg	280 (94)	135 (91)	145 (96)	0.10
Other lipid-lowering drugs				
Ezetimibe	10 (3)	4 (3)	6 (4)	0.75
Fibrates	0 (0)	0 (0)	0 (0)	
Niacin	0 (0)	0 (0)	0 (0)	
Resins	0 (0)	0 (0)	0 (0)	
Aspirin	285 (95)	140 (95)	145 (96)	0.59
Clopidogrel	38 (13)	20 (14)	18 (12)	0.73
Ticagrelor	192 (64)	91 (61)	101 (67)	0.34
Prasugrel	41 (14)	19 (13)	22 (15)	0.74
NOAC	16 (5)	11 (7)	5 (3)	0.13
Vitamin K antagonists	8 (3)	4 (3)	4 (3)	1.00

NOAC = new oral anticoagulants.



**Appendix Table 3.** Completeness of follow-up and study drug administration in the EVOPACS trial

	<b>All patients (n=308)</b>	<b>Evolocumab (n=155)</b>	<b>Placebo (n=153)</b>	<b>p value</b>
<b>Baseline (index hospitalization)</b>				
Study drug				
Refused injection and withdrew consent	1 (0.3%)	0 (0.0%)	1 (0.7%)	0.50
Double-blind injection of study drug	307 (99.7%)	155 (100.0%)	152 (99.3%)	0.50
<b>Week 4</b>				
Clinical visit	283 (91.9%)	137 (88.4%)	146 (95.4%)	0.035
No clinical visit	25 (8.1%)	18 (11.6%)	7 (4.6%)	0.035
Alive but did not want to come clinical visit	22 (7.1%)	16 (10.3%)	6 (3.9%)	0.044
Patient had withdrawn consent earlier	1 (0.3%)	0 (0.0%)	1 (0.7%)	0.50
Patient deceased	2 (0.6%)	2 (1.3%)	0 (0.0%)	0.50
Study drug				
Double-blind injection of study drug	279 (90.6%)	135 (87.1%)	144 (94.1%)	0.05
<b>Week 8</b>				
Clinical visit	293 (95.1%)	142 (91.6%)	151 (98.7%)	0.006
No clinical visit	15 (4.9%)	13 (8.4%)	2 (1.3%)	0.006
Alive but did not want to come to the clinic	12 (3.9%)	11 (7.1%)	1 (0.7%)	0.005
Patient had withdrawn consent earlier	1 (0.3%)	0 (0.0%)	1 (0.7%)	0.50
Patient deceased	2 (0.6%)	2 (1.3%)	0 (0.0%)	0.50

**Appendix Table 4.** Pre-specified sensitivity analysis of the primary endpoint, percentage change in calculated LDL-C from baseline to 8 weeks, using multiple imputations\*

	All patients	Evolocumab	Placebo	Mean difference (95% confidence intervals)†	p value
<b>Calculated LDL-C</b>					
% Change from baseline to week 8	-55.30% (-58.77% to -51.83%)	-74.16% (-77.65% to -70.66%)	-36.06% (-40.37% to -31.76%)	-37.15% (-42.13% to -32.18%)	<0.001

\* According to the protocol, a sensitivity analysis for the primary endpoint using multiple imputation to impute the primary endpoint was pre-specified if calculated LDL-C at 8 weeks was missing in more than 5% of the patients. Calculated LDL-C was not available at week 8 in 18 patients (5.8% of all 308 randomised patients).

P-value of the randomised arm, using mixed models correcting for a random effect of the site and a fixed effect of stable statin treatment 4 weeks before randomisation. Computations based on combining the results from 20 multiple imputed data sets using Rubin's rule. Imputations based on predictive mean matching to five nearest neighbours, using the following baseline variables: corneal arcus, xanthomas, thyroid dysfunction, eGFR, AST, ALT, ALP, ADP, TRAP, age, gender, BMI, systolic BP, diastolic BP; family history of CAD, peripheral arterial disease, diabetes mellitus, insulin-treated diabetes mellitus, arterial hypertension, hypercholesterolemia, smoking history, active smoker, history of MI, PCI, CABG, CAD, HF, stroke, TIA, malignancy, no vs medium vs high intensity statins in the 4 weeks before randomisation; and follow-up variables: clinical visit week 4, clinical visit week 8, adverse event leading to study drug discontinuation; lipid measurements imputed for baseline, week 4 and week 8 (if missing).

† Evolocumab minus placebo.

**Appendix Table 5.** Exploratory analysis of the primary endpoint using calculated LDL-C, or directly measured LDL-C in cases of calculated LDL-C <40mg/dL or triglycerides >400 mg/dL

	All patients	Evolocumab	Placebo	Mean difference (95% confidence intervals)*	p value
<b>Calculated or directly measured LDL-C</b>					
Baseline (mmol/L)	3.53 ± 0.98 [306]	3.61 ± 0.99 [154]	3.44 ± 0.96 [152]	0.12 (-0.06 to 0.30)	0.20
Week 8 (mmol/L)	1.53 ± 0.78 [291]	0.95 ± 0.44 [141]	2.07 ± 0.62 [150]	-1.11 (-1.23 to -0.99)	<0.001
Absolute change from baseline (mmol/L)	-1.99 ± 1.21 [290]	-2.66 ± 1.00 [140]	-1.37 ± 1.05 [150]	-1.24 (-1.44 to -1.04)	<0.001
% Change from baseline	-53.08% ± 28.29% [290]	-71.89% ± 15.35% [140]	-35.52% ± 26.25% [150]	-35.32% (-39.61% to -31.02%)	<0.001
LDL-C < 1.8 mmol/L at Week 8	66.0% [291]	95.7% [141]	38.0% [150]	57.9% (49.4% to 66.5%)	<0.001

Data expressed as means ± standard deviations or n (%)

\* Evolocumab minus placebo.

**Appendix Table 6.** Changes in lipids

	All patients	Evolocumab	Placebo	Mean difference (95% confidence intervals)	p value
Cholesterol at baseline (mmol/L)	5.41 ± 1.07 [306]	5.50 ± 1.11 [154]	5.31 ± 1.04 [152]	0.14 (-0.06 to 0.35)	0.17
Cholesterol at week 4 (mmol/L)	3.20 ± 0.92 [280]	2.56 ± 0.57 [136]	3.80 ± 0.76 [144]	-1.23 (-1.39 to -1.08)	<0.001
Absolute change from baseline (mmol/L)	-2.22 ± 1.30 [280]	-2.94 ± 1.08 [136]	-1.53 ± 1.10 [144]	-1.36 (-1.58 to -1.15)	<0.001
% Change from baseline	-39.02% ± 19.83% [280]	-52.12% ± 12.61% [136]	-26.65% ± 17.31% [144]	-24.72% (-27.71% to -21.73%)	<0.001
Cholesterol at week 8 (mmol/L)	3.26 ± 0.97 [291]	2.59 ± 0.66 [141]	3.89 ± 0.78 [150]	-1.29 (-1.46 to -1.13)	<0.001
Absolute change from baseline (mmol/L)	-2.15 ± 1.38 [290]	-2.94 ± 1.13 [140]	-1.42 ± 1.17 [150]	-1.46 (-1.69 to -1.23)	<0.001
% Change from baseline	-37.64% ± 21.98% [290]	-51.79% ± 14.62% [140]	-24.44% ± 19.33% [150]	-26.49% (-29.86% to -23.12%)	<0.001
HDL-C at baseline (mmol/L)	1.12 ± 0.29 [306]	1.11 ± 0.29 [154]	1.14 ± 0.29 [152]	-0.03 (-0.10 to 0.03)	0.30
HDL-C at week 4 (mmol/L)	1.16 ± 0.32 [280]	1.17 ± 0.32 [136]	1.15 ± 0.32 [144]	0.01 (-0.06 to 0.09)	0.72
Absolute change from baseline (mmol/L)	0.04 ± 0.19 [280]	0.07 ± 0.18 [136]	0.02 ± 0.19 [144]	0.05 (0.01 to 0.09)	0.02
% Change from baseline	4.68% ± 15.95% [280]	7.07% ± 15.92% [136]	2.42% ± 15.70% [144]	4.67% (0.97% to 8.36%)	0.01
HDL-C at week 8 (mmol/L)	1.19 ± 0.32 [291]	1.20 ± 0.33 [141]	1.18 ± 0.32 [150]	0.02 (-0.05 to 0.09)	0.56
Absolute change from baseline (mmol/L)	0.07 ± 0.21 [290]	0.09 ± 0.19 [140]	0.04 ± 0.22 [150]	0.05 (0.01 to 0.10)	0.02
% Change from baseline	7.12% ± 18.98% [290]	9.54% ± 17.90% [140]	4.87% ± 19.73% [150]	4.82% (0.50% to 9.14%)	0.03
Triglycerides at baseline (mmol/L)	1.74 ± 1.07 [306]	1.82 ± 1.24 [154]	1.65 ± 0.86 [152]	0.18 (-0.06 to 0.42)	0.14
Triglycerides at week 4 (mmol/L)	1.39 ± 0.62 [280]	1.33 ± 0.62 [136]	1.43 ± 0.63 [144]	-0.09 (-0.23 to 0.06)	0.23
Absolute change from baseline (mmol/L)	-0.35 ± 0.88 [280]	-0.50 ± 0.99 [136]	-0.22 ± 0.73 [144]	-0.28 (-0.48 to -0.08)	0.007
% Change from baseline	-6.29% ± 50.38% [280]	-14.80% ± 38.85% [136]	1.75% ± 58.25% [144]	-16.38% (-27.94% to -4.83%)	0.005
Triglycerides at week 8 (mmol/L)	1.39 ± 0.73 [291]	1.33 ± 0.72 [141]	1.44 ± 0.74 [150]	-0.10 (-0.26 to 0.07)	0.25
Absolute change from baseline (mmol/L)	-0.37 ± 1.03 [290]	-0.53 ± 1.12 [140]	-0.21 ± 0.92 [150]	-0.31 (-0.55 to -0.08)	0.009
% Change from baseline	-5.61% ± 76.73% [290]	-16.41% ± 40.39% [140]	4.46% ± 98.42% [150]	-20.04% (-37.43% to -2.65%)	0.02
Non-HDL-C at baseline (mmol/L)	4.28 ± 1.08 [306]	4.40 ± 1.13 [154]	4.17 ± 1.02 [152]	0.18 (-0.03 to 0.39)	0.098

Non-HDL-C at week 4 (mmol/L)	2.04 ± 0.89 [280]	1.39 ± 0.55 [136]	2.65 ± 0.69 [144]	-1.25 (-1.39 to -1.11)	<0.001
Absolute change from baseline (mmol/L)	-2.26 ± 1.30 [280]	-3.01 ± 1.07 [136]	-1.55 ± 1.08 [144]	-1.42 (-1.63 to -1.20)	<0.001
% Change from baseline	-50.10% ± 24.01% [280]	-67.16% ± 13.16% [136]	-33.98% ± 20.57% [144]	-32.30% (-35.69% to -28.92%)	<0.001
Non-HDL-C at week 8 (mmol/L)	2.07 ± 0.95 [291]	1.39 ± 0.61 [141]	2.71 ± 0.73 [150]	-1.32 (-1.47 to -1.16)	<0.001
Absolute change from baseline (mmol/L)	-2.22 ± 1.38 [290]	-3.03 ± 1.12 [140]	-1.46 ± 1.16 [150]	-1.52 (-1.74 to -1.29)	<0.001
% Change from baseline	-48.85% ± 26.82% [290]	-67.26% ± 15.37% [140]	-31.68% ± 23.65% [150]	-34.57% (-38.51% to -30.63%)	<0.001
Lipoprotein(a) at baseline (nmol/L)	68.56 ± 89.25 [305]	73.93 ± 94.49 [153]	63.16 ± 83.62 [152]	11.62 (-8.27 to 31.52)	0.25
Lipoprotein(a) at week 8 (nmol/L)	69.09 ± 93.81 [291]	69.77 ± 97.23 [141]	68.44 ± 90.80 [150]	1.54 (-20.00 to 23.08)	0.89
Absolute change from baseline (nmol/L)	0.89 ± 29.97 [289]	-4.55 ± 32.95 [139]	5.92 ± 26.03 [150]	-10.93 (-17.64 to -4.22)	0.001
% Change from baseline	5.64% ± 121.47% [289]	0.51% ± 67.61% [139]	10.40% ± 49.54% [150]	-10.37% (-38.33% to 17.59%)	0.47
Apolipoprotein B at baseline (g/L)	1.14 ± 0.29 [302]	1.17 ± 0.29 [151]	1.12 ± 0.29 [151]	0.04 (-0.02 to 0.09)	0.17
Apolipoprotein B at week 8 (g/L)	0.59 ± 0.25 [291]	0.41 ± 0.17 [141]	0.76 ± 0.20 [150]	-0.35 (-0.39 to -0.31)	<0.001
Absolute change from baseline (g/L)	-0.55 ± 0.35 [286]	-0.76 ± 0.28 [137]	-0.36 ± 0.31 [149]	-0.39 (-0.45 to -0.33)	<0.001
% Change from baseline	-45.45% ± 26.36% [286]	-63.62% ± 14.88% [137]	-28.75% ± 23.41% [149]	-34.18% (-38.21% to -30.16%)	<0.001
Apolipoprotein A1 at baseline (g/L)	1.34 ± 0.23 [301]	1.33 ± 0.23 [151]	1.36 ± 0.24 [150]	-0.04 (-0.09 to 0.01)	0.14
Apolipoprotein A1 at week 8 (g/L)	1.40 ± 0.26 [291]	1.40 ± 0.27 [141]	1.40 ± 0.25 [150]	0.00 (-0.05 to 0.06)	0.91
Absolute change from baseline (g/L)	0.05 ± 0.19 [285]	0.06 ± 0.19 [137]	0.03 ± 0.19 [148]	0.03 (-0.01 to 0.08)	0.16
% Change from baseline	4.49% ± 15.10% [285]	5.60% ± 15.47% [137]	3.47% ± 14.73% [148]	2.24% (-1.24% to 5.72%)	0.21

**Appendix Table 7.** Total number of events (with rate of events per patient-month at risk in brackets)

	No. of events	All patients Rate / person-months	No. of events	Evolocumab Rate / person-months	No. of events	Placebo Rate / person-months	Incidence Rate Ratio [Evolocumab/Placebo]	p value
	n=307	573.6 person-months	n=155	284.1 person-months	n=152*	289.5 person-months		
Any adverse event	258	0.450 (0.398-0.508)	144	0.507 (0.431-0.596)	114	0.394 (0.328-0.473)	1.37 (1.04-1.80)	0.025
Non-serious adverse event	229	0.399 (0.351-0.454)	127	0.447 (0.376-0.532)	102	0.352 (0.290-0.428)	1.34 (1.00-1.79)	0.049
Serious adverse event	29	0.051 (0.035-0.073)	17	0.060 (0.037-0.096)	12	0.041 (0.024-0.073)	1.54 (0.65-3.62)	0.32
Adverse event resulting in study drug discontinuation	5	0.009 (0.004-0.021)	2	0.007 (0.002-0.028)	3	0.010 (0.003-0.032)	0.68 (0.11-4.07)	0.672
Events of special interest								
ALT increase >3x ULN	4	0.007 (0.003-0.019)	2	0.007 (0.002-0.028)	2	0.007 (0.002-0.028)	1.02 (0.14-7.24)	0.98
Symptomatic overdose	0		0		0			
General allergic reaction	1	0.002 (0.000-0.012)	1	0.004 (0.000-0.025)	0			1.00
Local injection site reaction	9	0.016 (0.008-0.030)	5	0.018 (0.007-0.042)	4	0.014 (0.005-0.037)	1.19 (0.28-5.06)	0.81
Pregnancy	0		0		0			
Neurocognitive event	1	0.002 (0.000-0.012)	1	0.004 (0.000-0.025)	0			1.00
Musculoskeletal pain	14	0.024 (0.014-0.041)	9	0.032 (0.016-0.061)	5	0.017 (0.007-0.041)	1.80 (0.58-5.64)	0.31
Nasopharyngitis	7	0.012 (0.006-0.026)	4	0.014 (0.005-0.038)	3	0.010 (0.003-0.032)	1.36 (0.30-6.07)	0.69
Diarrhoea	10	0.017 (0.009-0.032)	7	0.025 (0.012-0.052)	3	0.010 (0.003-0.032)	2.40 (0.57-10.11)	0.23
Other	183	0.319 (0.276-0.369)	98	0.345 (0.283-0.421)	85	0.294 (0.237-0.363)	1.22 (0.89-1.67)	0.22
Positively adjudicated events								
All-cause death	2	0.003 (0.001-0.014)	2	0.007 (0.002-0.028)	0			
Cardiovascular death	2	0.003 (0.001-0.014)	2	0.007 (0.002-0.028)	0			
Myocardial infarction	5	0.009 (0.004-0.021)	4	0.014 (0.005-0.038)	1	0.003 (0.000-0.025)	4.08 (0.46-36.47)	0.21
Coronary revascularisation	79	0.138 (0.110-0.172)	39	0.137 (0.100-0.188)	40	0.138 (0.101-0.188)	0.99 (0.64-1.54)	0.98
Target-lesion revascularisation	1	0.002 (0.000-0.012)	0		1	0.003 (0.000-0.025)		
Staged	76	0.132 (0.106-0.166)	37	0.130 (0.094-0.180)	39	0.135 (0.098-0.184)	0.97 (0.62-1.52)	0.88

Other revascularisation	2	0.003 (0.001-0.014)	2	0.007 (0.002-0.028)	0	0.50
Cerebrovascular Event	1	0.002 (0.000-0.012)	1	0.004 (0.000-0.025)	0	1.00
Hospitalization for recurrent ACS	1	0.002 (0.000-0.012)	0		1	0.003 (0.000-0.025)
Hospitalization for heart failure	0		0		0	0.50

Rate ratios are estimated using the Poisson regression with two-sided p-values from Wald test. Fisher's exact test on the raw counts in case no events in one randomised treatment arm.

ACS = acute coronary syndrome; ALT = alanine aminotransferase; ULN = upper limit of normal.

\* Excluded is one patient randomly allocated to placebo who immediately withdrew consent and refused study drug administration.

**Appendix Table 8.** Description of adverse events that resulted in study drug discontinuation in five patients

Patient	Randomised arm	Study drug administrations	Description of adverse event	Blinded assessment of relationship of adverse event with study drug *	Serious adverse event
Patient # 1	Evolocumab	Administered at baseline but not at week 4.	<p>69-year old male patient presented with NSTEMI-ACS. Coronary artery bypass surgery was performed 3 days after study enrolment and baseline study drug administration. The patient was discharged 12 days after study enrolment and received aspirin and rivaroxaban due to newly (in-hospital) diagnosed atrial fibrillation. At 27 days after study enrolment the patient was hospitalized in another hospital with anemia (hemoglobin drop from 11.9 to 7.8 g/L) and gastrointestinal bleeding. The patient received erythrocyte transfusion, and rivaroxaban was discontinued.</p> <p>The week 4 clinical visit and week 4 study drug administration were not performed, as the patient was hospitalized in another hospital during the allowed time window. The patient returned for the week 8 clinical visit.</p>	<ul style="list-style-type: none"> <li>Local Investigator: No/Unlikely</li> <li>DSMB: No/Unlikely</li> </ul>	Yes
Patient #2	Evolocumab	Administered at baseline but not at week 4.	<p>71-year old male patient presented with acute STEMI. Coronary artery bypass surgery was performed 4 days after study enrolment and baseline study drug administration. The patient was discharged 10 days after study enrolment. 11 days later (i.e. 21 days after study enrolment) the patient presented to the emergency room with pleural pain and fever and was hospitalized for pleural effusion presumably in the context of post-operative Dressler syndrome. Pleural puncture resulted in iatrogenic hemo- and pneumothorax that prolonged hospitalization. During the hospitalization, the patient was further diagnosed with herpes simplex type 1 infection, necessitating treatment with acyclovir.</p> <p>The week 4 clinical visit and week 4 study drug administration were not performed, as the patient was hospitalized during the allowed time window. The patient did not return for the week 8 clinical visit.</p>	<ul style="list-style-type: none"> <li>Local Investigator: No/Unlikely</li> <li>DSMB: No/Unlikely</li> </ul>	Yes
Patient #3	Placebo	Administered at baseline but not at week 4.	<p>51-year old male patient presented with acute anterior STEMI and underwent primary PCI with stenting of the mid left anterior descending artery. At 25 days after study enrolment and baseline study drug administration, the patient was hospitalized for suspected upper gastrointestinal bleeding (melena and anemia). Endoscopic control showed erosive gastritis. The patient received erythrocyte transfusion, was stabilized and discharged after 8 days (day 33 after study enrolment).</p> <p>The week 4 clinical visit and week 4 study drug administration were not performed, as the patient was hospitalized during the allowed time window. The patient returned for the week 8</p>	<ul style="list-style-type: none"> <li>Local Investigator: No/Unlikely</li> <li>DSMB: No/Unlikely</li> </ul>	Yes



			clinical visit.		
Patient #4	Placebo	Administered at baseline but not at week 4.	68-year old male patient presented with acute STEMI and underwent primary PCI. The patient reported persistent cough that started 7 days after study enrolment and baseline study drug administration. The patient consulted his general practitioner, who recommended stopping the ACE-inhibitor (ramipril). Because the symptoms had not improved at the week-4 study visit, it was decided not to perform the study drug administration.  The patient returned for the week 8 clinical visit.	N/A *	No
Patient #5	Placebo	Administered at baseline but not at week 4.	54-year old male patient presented with acute NSTEMI-ACS and underwent PCI. The patient reported a rash 5 days following study enrolment and baseline study drug administration. The rash disappeared 5 days later with no medical treatment (only moisturizing cream was applied locally).  The week-4 study visit was performed, but the local investigator advised against the administration of the week-4 study drug. The patient returned for the week 8 clinical visit.	N/A *	No

DSM = Data and Safety Monitoring Board.

\* As per protocol, the relationship between an adverse event and the study drug was assessed by the local investigator as well as the DSMB in case of reported serious adverse events.

**Appendix Table 9.** Narratives for two deaths that occurred during the EVOPACS study

Patient	Randomised arm	Description	Blinded assessment of relationship of death with study drug
Patient # 1	Evolocumab	<p>A 75-year-old male patient with known coronary artery disease (history of myocardial infarction and PCI) presented with NSTEMI-ACS. Symptoms had reportedly began 2 days before. Cardiovascular risk factors included active smoking, diabetes mellitus, arterial hypertension, and hypercholesterolemia (LDL cholesterol 2.8 mmol/l at baseline under atorvastatin 20mg). Baseline medical treatment included aspirin, amlodipin, lisinopril, and atorvastatin. The patient was enrolled in the study and received the baseline study drug on the same day of admission in the hospital. Coronary angiography showed complex three-vessel coronary artery disease (chronic occlusion of the right coronary artery, significant stenoses in the proximal left anterior descending artery and first marginal branch). The patient was scheduled for coronary artery bypass surgery after 7 days, and remained in-hospital. On the day of the scheduled surgery (day 7 after study enrolment), the patient reported retrosternal pain. ECG showed ST elevation in anterior and inferior leads. The patient underwent urgent coronary angiography, which showed acute occlusion of the proximal left anterior descending artery, occlusion of the right circumflex artery, and a critical lesion in the first marginal branch. The patient developed cardiogenic shock and, during attempted recanalization of the left anterior descending artery, developed rhythm disorders and cardiac arrest. Despite resuscitation (30 minutes compression) and attempted extracorporeal membrane oxygenation (ECMO), the patient died with electromechanical dissociation.</p> <p>The CEC adjudicated the death as cardiovascular.</p>	<ul style="list-style-type: none"> <li>Local Investigator: No/Unlikely</li> <li>DSMB: No/Unlikely</li> </ul>
Patient #2	Evolocumab	<p>A 76-year-old patient with a history of atrial fibrillation presented with NSTEMI-ACS. Cardiovascular risk factors included arterial hypertension, obesity (BMI 32.6), and hypercholesterolemia (LDL-C 3.86 mmol/l under no lipid-lowering therapy). The patient was enrolled in the study and received the baseline study drug on the same day of hospital admission, on the same day and following the performance of coronary angiography. Angiography showed complex three-vessel disease, and aortic valve stenosis was found in echocardiography with preserved left ventricular function (LVEF 58%). The patient was transferred to another hospital for performance of cardiac surgery. The patient remained in-hospital, and surgery (quadruple coronary bypass grafting and concomitant aortic valve replacement) was performed at 11 days after study enrolment. Surgery was complicated by intraoperative rupture of the calcific aortic root and the right coronary ostium requiring composite graft implantation (Bentall procedure) with re-implantation of the right coronary artery using a short saphenous venous graft. Postoperatively the patient remained hemodynamically unstable requiring hemodynamic support with a veno-arterial extracorporeal membrane oxygenation device (ECMO), and underwent two repeat surgical revisions for pericardial tamponade. Right ventricular failure was the leading presentation. Coronary angiography six days after surgery (17 days after study enrolment) revealed an occluded venous graft to the right coronary artery; however, no repeat revascularization was attempted. Progressive cardiogenic shock with multi-organ failure (ischemic hepatic failure, acute kidney failure requiring hemodialysis) evolved and six days later, replacement of the veno-arterial ECMO by a percutaneous right ventricular assist device was attempted. This immediately</p>	<ul style="list-style-type: none"> <li>Local Investigator: No/Unlikely</li> <li>DSMB: No/Unlikely</li> </ul>

		resulted in acute left ventricular decompensation refractory to further medical treatment. The patient died 14 days after surgery (25 days after study enrolment).  The CEC adjudicated the death as cardiovascular.	
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CEC = Clinical Events Committee; DSMB = Data and Safety Monitoring Board.

**Appendix Table 10.** Narratives for adjudicated myocardial infarctions that occurred in five patients during the EVOPACS study

Patient	Randomised arm	Description	Blinded assessment of relationship of death with study drug *
Patient # 1	Evolocumab	<p>An 81-year-old female patient without known coronary artery disease presented with NSTEMI-ACS. Cardiovascular risk factors included previous smoking and hypercholesterolemia (LDL cholesterol 4.1 mmol/l at baseline under no statin treatment). The patient had not been on regular medical treatment at the time of study enrolment. Coronary angiography was performed on the day of study enrolment and showed three-vessel coronary artery disease; the culprit lesion in the right coronary artery was treated with PCI at baseline. Additional significant stenoses in the proximal and mid left anterior descending artery and in the proximal left circumflex artery were scheduled for an elective, staged PCI after 4 weeks. The elective cardiac catheterization occurred 28 days after the index procedure (study day 28). The lesions identified at the index procedure were treated by means of stenting with a total of 5 drug-eluting stents. Laboratory control on the following day (study day 29) showed significant increase in cardiac biomarkers (high-sensitivity troponin).</p> <p>This event was not reported as a myocardial infarction by the investigators and was therefore not evaluated by the DSMB. The event (occurring on study day 29) was adjudicated by the CEC as a case of myocardial infarction.</p>	<ul style="list-style-type: none"> <li>Local Investigator: n/a</li> <li>DSMB: n/a</li> </ul>
Patient #2	Placebo	<p>A 71-year-old female patient with known known coronary artery disease (history of PCI in the left anterior descending artery) presented with NSTEMI-ACS. Cardiovascular risk factors included arterial hypertension, obesity (BMI 31.0), and hypercholesterolemia (screening LDL-C 5.9 mmol/l under no lipid-lowering therapy). The patient was enrolled in the study and received the baseline study drug on the same day and following the performance of coronary angiography. Coronary angiography identified a significant restenotic lesion in the proximal left anterior descending artery (in-stent restenosis) as the culprit lesion of the index event. The lesion was treated by means of dilatation with a drug-eluting balloon, without implantation of a stent. The patient was discharged on the following day (one day after study enrolment and coronary angiography). The patient returned 28 days after study enrolment for the week-4 clinical visit (study drug administration and week-4 laboratory testing). Four days after the week-4 visit (32 days after study enrolment), the patient experienced symptoms of chest pain, and laboratory testing showed significant increase of cardiac biomarkers. A diagnosis of NSTEMI-ACS was made. Coronary angiography on study day 33 showed a significant restenotic lesion in the proximal left anterior descending artery / first diagonal branch bifurcation that was treated with PCI and implantation of drug-eluting stents.</p> <p>The event was reported by the local investigators as myocardial infarction treated with PCI. The CEC adjudicated the event as myocardial infarction, repeat coronary revascularization (target-lesion revascularization), and hospitalization for recurrent ACS.</p> <p>The patient returned for the week-8 clinical visit 60 days after study enrolment.</p>	<ul style="list-style-type: none"> <li>Local Investigator: No/Unlikely</li> <li>DSMB: No/Unlikely</li> </ul>

Patient #3	Evolocumab	<p>A 51-year-old male patient without known known coronary artery disease presented with NSTEMI-ACS. Cardiovascular risk factors included arterial hypertension, active smoking, and hypercholesterolemia (screening LDL-C 3.3 mmol/l under no lipid-lowering therapy). The patient was enrolled in the study and received the baseline study drug on the same day and prior to the performance of coronary angiography. Coronary angiography showed significant stenoses in the mid left anterior descending artery, proximal left circumflex artery and first marginal branch. Coronary artery bypass surgery was decided after discussion within the heart team and with the patient, but eventually due to clinical instability, it was decided to proceed with percutaneous revascularization in two steps. Two days after study enrolment and after the first coronary angiography, angioplasty in the left anterior descending artery was performed with implantation of two drug-eluting stents. Four days later (six days after enrolment in the study) the lesions in the left circumflex artery and first marginal branch were treated with angioplasty and stenting. On the same day and following the intervention (study day 6), the patient developed retrosternal chest pain, with increase of cardiac enzymes and new ECG changes. The patient was treated with optimization of medical therapy. Repeat coronary angiography was performed on study day 12 that showed significant stenoses in the first marginal branch and distal circumflex artery that were treated with PCI.</p> <p>A myocardial infarction event was not reported by the local investigators and was therefore not evaluated by the DSMB. The CEC adjudicated the event occurring on study day 6 as myocardial infarction.</p> <p>The patient returned for the week-4 visit 28 days after study enrolment, and for the week-8 clinical visit 61 days after study enrolment.</p>	<ul style="list-style-type: none"> <li>Local Investigator: n/a</li> <li>DSMB: n/a</li> </ul>
Patient #4	Evolocumab	<p>This event occurred in a patient who died (see patient #1 in Appendix Table 9).</p> <p>A 75-year-old male patient with known coronary artery disease (history of myocardial infarction and PCI) presented with NSTEMI-ACS. Symptoms had reportedly began 2 days before. Cardiovascular risk factors included active smoking, diabetes mellitus, arterial hypertension, and hypercholesterolemia (LDL cholesterol 2.8 mmol/l at baseline under atorvastatin 20mg). Baseline medical treatment included aspirin, amlodipin, lisinopril, and atorvastatin. The patient was enrolled in the study and received the baseline study drug on the same day of admission in the hospital, Coronary angiography showed complex three-vessel coronary artery disease (chronic occlusion of the right coronary artery ,significant stenoses in the proximal left anterior descending artery and first marginal branch). The patient was scheduled for coronary artery bypass surgery after 7 days, and remained in-hospital. On the day of the scheduled surgery (day 7 after study enrolment), the patient reported retrosternal pain. ECG showed ST elevation in anterior and inferior leads. The patient underwent urgent coronary angiography, which showed acute occlusion of the proximal left anterior descending artery, occlusion of the right circumflex artery, and a critical lesion in the first marginal branch. The patient developed cardiogenic shock and, during attempted recanalization of the left anterior descending artery, developed rhythm disorders and cardiac arrest. Despite resuscitation (30 minutes compression) and attempted extracorporeal membrane oxygenation (ECMO), the patient died with electromechanical dissociation.</p> <p>The event was reported by the local investigators as myocardial infarction and adjudicated by the CEC as myocardial infarction.</p>	<ul style="list-style-type: none"> <li>Local Investigator: No/unlikely</li> <li>DSMB: No/unlikely</li> </ul>

Patient #5	Evolocumab	<p>This event occurred in a patient who died (see patient #2 in Appendix Table 9).</p> <p>A 76-year-old patient with a history of atrial fibrillation presented with NSTEMI-ACS. Cardiovascular risk factors included arterial hypertension, obesity (BMI 32.6), and hypercholesterolemia (LDL-C 3.86 mmol/l under no lipid-lowering therapy). The patient was enrolled in the study and received the baseline study drug on the same day of hospital admission, on the same day and following the performance of coronary angiography. Angiography showed complex three-vessel disease, and aortic valve stenosis was found in echocardiography with preserved left ventricular function (LVEF 58%). The patient was transferred to another hospital for performance of cardiac surgery. The patient remained in-hospital, and surgery (quadruple coronary bypass grafting and concomitant aortic valve replacement) was performed at 11 days after study enrolment. Surgery was complicated by intraoperative rupture of the calcific aortic root and the right coronary ostium requiring composite graft implantation (Bentall procedure) with re-implantation of the right coronary artery using a short saphenous venous graft. Postoperatively the patient remained hemodynamically unstable requiring hemodynamic support with a veno-arterial extracorporeal membrane oxygenation device (ECMO), and underwent two repeat surgical revisions for pericardial tamponade. Right ventricular failure was the leading presentation. Coronary angiography six days after surgery (17 days after study enrolment) revealed an occluded venous graft to the right coronary artery; however, no repeat revascularization was attempted. Progressive cardiogenic shock with multi-organ failure (ischemic hepatic failure, acute kidney failure requiring hemodialysis) evolved and six days later, replacement of the veno-arterial ECMO by a percutaneous right ventricular assist device was attempted. This immediately resulted in acute left ventricular decompensation refractory to further medical treatment. The patient died 14 days after surgery (25 days after study enrolment).</p> <p>A myocardial infarction event was not reported by the local investigators and was therefore not evaluated by the DSMB. The CEC adjudicated the event occurring on study day 17 (six days after surgery, day of performance of the repeat coronary angiography) as myocardial infarction.</p>	<ul style="list-style-type: none"> <li>Local Investigator: n/a</li> <li>DSMB: n/a</li> </ul>

CEC = Clinical Events Committee; DSMB = Data and Safety Monitoring Board; n/a = not applicable; PCI = percutaneous coronary intervention.

\* As per protocol, the relationship between an adverse event and the study drug was assessed by the local investigator as well as the DSMB in case of reported serious adverse events.

**Appendix Table 11.** Outcomes for inflammatory biomarkers

	All patients	Evolocumab	Placebo	Mean difference	p value
<b>hs-CRP</b>					
Baseline (mg/L)	6.65 ± 5.98 [305]	6.68 ± 5.89 [153]	6.63 ± 6.09 [152]	0.06 (-1.28 to 1.40)	0.93
Week 8 (mg/L)	2.46 ± 3.48 [291]	2.69 ± 3.83 [141]	2.23 ± 3.11 [150]	0.46 (-0.34 to 1.26)	0.26
Absolute change (baseline to week 8)	-3.99 ± 6.53 [289]	-3.47 ± 6.53 [139]	-4.47 ± 6.51 [150]	0.98 (-0.52 to 2.48)	0.20
% Change (baseline to week 8)	-25.35 ± 194.67	-14.87 ± 255.75 [139]	-35.07 ± 111.67 [150]	19.65 (-25.16 to 64.46)	0.39
hs-CRP level <2 mg/L at week 8 (%)	69.1% [291]	68.8% [141]	69.3% [150]	-0.7% (9.9% to -11.4%)	0.89
<b>Interleukin-1β</b>					
Baseline (pg/ml)	n = 302, 1.07 ± 0.72	n = 151, 1.06 ± 0.85	n = 151, 1.08 ± 0.57	-0.02 (-0.18 to 0.15)	0.85
Week 8 (pg/ml)	n = 289, 1.12 ± 1.45	n = 140, 1.16 ± 1.94	n = 149, 1.09 ± 0.74	0.07 (-0.27 to 0.40)	0.70
Change (baseline to week 8) (pg/ml)	n = 284, 0.02 ± 0.89	n = 136, 0.05 ± 0.90	n = 148, -0.01 ± 0.89	0.06 (-0.14 to 0.27)	0.55
<b>Interleukin 6 (pg/ml)</b>					
Baseline (pg/ml)	n = 303, 13.66 ± 15.50	n = 151, 14.58 ± 13.87	n = 152, 12.75 ± 16.97	1.85 (-1.62 to 5.32)	0.30
Week 8 (pg/ml)	n = 289, 3.78 ± 5.34	n = 140, 4.02 ± 6.08	n = 149, 3.55 ± 4.56	0.49 (-0.74 to 1.72)	0.43
Change (baseline to week 8) (pg/ml)	n = 285, 9.63 ± 14.92	n = 136, 9.95 ± 14.62	n = 149, 9.34 ± 15.23	0.59 (-2.87 to 4.05)	0.74

Data expressed as mean ± standard deviation or n (%). P-value of the randomised arm, using mixed models correcting for a random effect of the site and a fixed effect of stable statin treatment 4 weeks before randomisation.

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